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Capecitabine for hormone receptor-positive versus hormone receptor-negative breast cancer (Review)

Hoon SN, Lau PKH, White AM, Bulsara MK, Banks PD, Redfern AD

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[Intervention Review]

Capecitabine for hormone receptor-positive versus hormone receptor-negative breast cancer

Siao-Nge Hoon[1,2a], Peter K H Lau[2,3b], Alison M White[4,5], Max K Bulsara[6,7,8], Patricia D Banks[3,9], Andrew D Redfern[10,11]

[1]Medical Oncology Department, St John of God Midland, Perth, Australia. [2]Medical Oncology Department, Sir Charles Gairdner Hospital, Perth, Australia. [3]Medical Oncology Department, Peter MacCallum Cancer Centre, Melbourne, Australia. [4]Murdoch Community Hospice, St John of God Hospital Murdoch, Perth, Australia. [5]Palliative Care Department, Royal Perth Hospital, Perth, Australia. [6]Institute for Health Research, University of Notre Dame Australia, Fremantle, Australia. [7]School of Population and Global Health, The University of Western Australia, Perth, Australia. [8]Division of Surgery and Interventional Science, University College London, London, UK. [9]Medical Oncology Department, University Hospital Geelong, Geelong, Australia. [10]School of Medicine, University of Western Australia, Perth, Australia. [11]Medical Oncology Department, Fiona Stanley Hospital, Perth, Australia

[a]These authors contributed equally to this work. [b]These authors contributed equally to this work

Contact: Andrew D Redfern, andrew.redfern@health.wa.gov.au, andrew.redfern@optusnet.com.au.

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ABSTRACT

Background

Retrospective analyses suggest that capecitabine may carry superior activity in hormone receptor-positive relative to hormone receptor-negative metastatic breast cancer. This review examined the veracity of that finding and explored whether this differential activity extends to early breast cancer.

Objectives

To assess effects of chemotherapy regimens containing capecitabine compared with regimens not containing capecitabine for women with hormone receptor-positive versus hormone receptor-negative breast cancer across the three major treatment scenarios: neoadjuvant, adjuvant, metastatic.

Search methods

On 4 June 2019, we searched the Cochrane Breast Cancer Specialised Register; the Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 5) in the Cochrane Library; MEDLINE; Embase; the World Health Organization International Clinical Trials Registry Platform; and ClinicalTrials.gov.

Selection criteria

Randomised controlled trials looking at chemotherapy regimens containing capecitabine alone or in combination with other agents versus a control or similar regimen without capecitabine for treatment of breast cancer at any stage. The primary outcome measure for metastatic and adjuvant trials was overall survival (OS), and for neoadjuvant studies pathological complete response (pCR).

Data collection and analysis

Two review authors independently extracted data and assessed risk of bias and certainty of evidence using the GRADE approach. Hazard ratios (HRs) were derived for time-to-event outcomes, and odds ratios (ORs) for dichotomous outcomes, and meta-analysis was performed using a fixed-effect model.

Main results

We included 26 studies with outcome data by hormone receptor: 12 metastatic studies (n = 4325), 6 neoadjuvant trials (n = 3152), and 8 adjuvant studies (n = 13,457).

Capecitabine treatment was added in several different ways across studies. These could be classified as capecitabine alone compared to another treatment, capecitabine substituted for part of the control chemotherapy, and capecitabine added to control chemotherapy.

In the metastatic setting, the effect of capecitabine was heterogenous between hormone receptor-positive and -negative tumours. For OS, no difference between capecitabine-containing and non-capecitabine-containing regimens was observed for all participants taken together (HR 1.01, 95% confidence interval (CI) 0.98 to 1.05; 12 studies, 4325 participants; high-certainty evidence), for those with hormone receptor-positive disease (HR 0.93, 95% CI 0.84 to 1.04; 7 studies, 1834 participants; high-certainty evidence), and for those with hormone receptor-negative disease (HR 1.00, 95% CI 0.88 to 1.13; 8 studies, 1577 participants; high-certainty evidence). For progression-free survival (PFS), a small improvement was seen for all people (HR 0.89, 95% CI 0.82 to 0.96; 12 studies, 4325 participants; moderate-certainty evidence). This was largely accounted for by a moderate improvement in PFS for inclusion of capecitabine in hormone receptor-positive cancers (HR 0.82, 95% CI 0.73 to 0.91; 7 studies, 1594 participants; moderate-certainty evidence) compared to no difference in PFS for hormone receptor-negative cancers (HR 0.96, 95% CI 0.83 to 1.10; 7 studies, 1122 participants; moderate-certainty evidence). Quality of life was assessed in five studies; in general there did not seem to be differences in global health scores between the two treatment groups at around two years' follow-up.

Neoadjuvant studies were highly variable in design, having been undertaken to test various experimental regimens using pathological complete response (pCR) as a surrogate for disease-free survival (DFS) and OS. Across all patients, capecitabine-containing regimens resulted in little difference in pCR in comparison to non-capecitabine-containing regimens (odds ratio (OR) 1.12, 95% CI 0.94 to 1.33; 6 studies, 3152 participants; high-certainty evidence). By subtype, no difference in pCR was observed for either hormone receptor-positive (OR 1.22, 95% CI 0.76 to 1.95; 4 studies, 964 participants; moderate-certainty evidence) or hormone receptor-negative tumours (OR 1.28, 95% CI 0.61 to 2.66; 4 studies, 646 participants; moderate-certainty evidence). Four studies with 2460 people reported longer-term outcomes: these investigators detected no difference in either DFS (HR 1.02, 95% CI 0.86 to 1.21; high-certainty evidence) or OS (HR 0.97, 95% CI 0.77 to 1.23; high-certainty evidence).

In the adjuvant setting, a modest improvement in OS was observed across all participants (HR 0.89, 95% CI 0.81 to 0.98; 8 studies, 13,547 participants; moderate-certainty evidence), and no difference in OS was seen in hormone receptor-positive cancers (HR 0.86, 95% CI 0.68 to 1.09; 3 studies, 3683 participants), whereas OS improved in hormone receptor-negative cancers (HR 0.72, 95% CI 0.59 to 0.89; 5 studies, 3432 participants). No difference in DFS or relapse-free survival (RFS) was observed across all participants (HR 0.93, 95% CI 0.86 to 1.01; 8 studies, 13,457 participants; moderate-certainty evidence). As was observed for OS, no difference in DFS/RFS was seen in hormone receptor-positive cancers (HR 1.03, 95% CI 0.91 to 1.17; 5 studies, 5604 participants; moderate-certainty evidence), and improvements in DFS/RFS with inclusion of capecitabine were observed for hormone receptor-negative cancers (HR 0.74, 95% CI 0.64 to 0.86; 7 studies, 3307 participants; moderate-certainty evidence).

Adverse effects were reported across all three scenarios. When grade 3 or 4 febrile neutropenia was considered, no difference was seen for capecitabine compared to non-capecitabine regimens in neoadjuvant studies (OR 1.31, 95% CI 0.97 to 1.77; 4 studies, 2890 participants; moderate-certainty evidence), and a marked reduction was seen for capecitabine in adjuvant studies (OR 0.55, 95% CI 0.47 to 0.64; 5 studies, 8086 participants; moderate-certainty evidence). There was an increase in diarrhoea and hand-foot syndrome in neoadjuvant (diarrhoea: OR 1.95, 95% CI 1.32 to 2.89; 3 studies, 2686 participants; hand-foot syndrome: OR 6.77, 95% CI 4.89 to 9.38; 5 studies, 3021 participants; both moderate-certainty evidence) and adjuvant trials (diarrhoea: OR 2.46, 95% CI 2.01 to 3.01; hand-foot syndrome: OR 13.60, 95% CI 10.65 to 17.37; 8 studies, 11,207 participants; moderate-certainty evidence for both outcomes).

Authors' conclusions

In summary, a moderate PFS benefit by including capecitabine was seen only in hormone receptor-positive cancers in metastatic studies. No benefit of capecitabine for pCR was noted overall or in hormone receptor subgroups when included in neoadjuvant therapy. In contrast, the addition of capecitabine in the adjuvant setting led to improved outcomes for OS and DFS in hormone receptor-negative cancer. Future studies should stratify by hormone receptor and triple-negative breast cancer (TNBC) status to clarify the differential effects of capecitabine in these subgroups across all treatment scenarios, to optimally guide capecitabine inclusion.

PLAIN LANGUAGE SUMMARY

Benefits of capecitabine in hormone receptor-positive compared to hormone receptor-negative breast cancer

What is the aim of this review?

The aims of this Cochrane Review were to find out whether capecitabine is more useful in hormone receptor-positive or -negative breast cancers, and to see whether this differs depending on how advanced the cancer is. We collected and analysed all relevant studies to answer this question.

What was studied in the review?

Capecitabine is an anti-breast cancer drug in tablet form that has relatively few side effects in many people and can control cases of advanced breast cancer, sometimes for long periods. Some trials aiming to stop the return of cancer after treatment for early breast cancer also suggest modest benefits from adding capecitabine. We compared the use of capecitabine in breast cancer as palliative treatment (incurable metastatic or advanced disease), as neoadjuvant treatment (before surgery for early breast cancer), and as adjuvant treatment (after surgery for early breast cancer). We found a total of 26 studies, with 12 studies in the metastatic setting, 6 in the neoadjuvant setting, and 8 in the adjuvant setting. We found that capecitabine treatment was added in a number of different ways in different trials. These could be classified as monotherapy, where capecitabine alone was compared to another treatment (often another single drug); substitution, where capecitabine was used in place of another drug within a combined drug treatment; and addition, where capecitabine was added to standard treatment using one or more drugs.

Key messages

In the setting of advanced disease, there was a modest increase in time to cancer progression (how long cancer growth is stopped) with the addition of capecitabine in hormone receptor-positive but not in hormone receptor-negative breast cancer, although no survival benefit was seen in either group. However, when broken down by how capecitabine was added to the regimen, the addition of capecitabine to other chemotherapy was most effective, demonstrating both longer time to progression in both groups and improved survival in hormone receptor-positive cancers.

In the neoadjuvant setting, capecitabine-containing chemotherapy regimens showed no difference compared with non-capecitabine-containing chemotherapy regimens: no significant impact on the pathological complete response rate (the proportion of patients for whom all traces of cancer in the breast have been eradicated by treatment by the time of surgery), on disease-free survival (the number of people who remain cancer-free at a certain time after surgery), or on overall survival, regardless of hormone receptor subgroup.

In the adjuvant setting, there was a small benefit for overall survival with capecitabine-containing compared to non-capecitabine-containing chemotherapy regimens, when all patients were looked at together. In triple-negative and hormone receptor-negative breast cancers, reductions in both cancer return rates and deaths from breast cancer were substantial for capecitabine-containing chemotherapy regimens compared with non-capecitabine-containing regimens. In contrast, for hormone receptor-positive breast cancers, there was no significant impact of capecitabine on either cancer return rates or deaths from cancer.

The common side effects of capecitabine were as expected, with the most common being diarrhoea and hand-foot syndrome (redness, tightness, and discomfort or pain in the soles and palms).

How up-to-date is this review?

The review authors searched for studies that had been published up to June 2019.

SUMMARY OF FINDINGS

Summary of findings 1. Capecitabine-containing regimens compared to chemotherapy regimens without capecitabine for metastatic breast cancer

Capecitabine-containing regimens compared to chemotherapy regimens without capecitabine for metastatic breast cancer

Patient or population: people with metastatic breast cancer
Setting: outpatient
Intervention: capecitabine-containing regimens
Comparison: chemotherapy regimens without capecitabine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with chemotherapy regimens without capecitabine	Risk with capecitabine-containing regimens				
Overall survival (OS) median follow-up: range 18.6 months to 37.6 months	1-year risk of death[a] 367 per 1000	370 per 1000 (361 to 381)	HR 1.01 (0.98 to 1.05)	4325 (12 RCTs)	⊕⊕⊕⊕ HIGH	Heterogeneity was detected and was explained by variations in chemotherapy backbones. The certainty of evidence was not downgraded, as variations in chemotherapy are likely to occur in clinical practice
OS: hormone receptor-positive median follow-up: range 18.6 months to 37.6 months	1-year risk of death[a] 338 per 1000	310 per 1000 (281 to 343)	HR 0.90 (0.80 to 1.02)	1565 (6 RCTs)	⊕⊕⊕⊕ HIGH	As above
OS: hormone receptor-negative median follow-up: range 18.6 months to 34.3 months	1-year risk of death[a] 590 per 1000	608 per 1000 (556 to 657)	HR 1.05 (0.91 to 1.20)	1408 (7 RCTs)	⊕⊕⊕⊕ HIGH	As above
Progression-free survival (PFS) median follow-up: range 18.6 months to 37.6 months	1-year risk of progression[b] 745 per 1000	704 per 1000 (678 to 731)	HR 0.89 (0.83 to 0.96)	4325 (12 RCTs)	⊕⊕⊕⊝ MODERATE[c]	

PFS: hormone receptor-positive median follow-up: range 18.6 months to 37.6 months	1-year risk of progression[b]		HR 0.77 (0.68 to 0.87)	1372 (6 RCTs)	⊕⊕⊕⊝ MODERATE[c]	
	750 per 1000	656 per 1000 (610 to 701)				
PFS: hormone receptor-negative median follow-up: range 20.6 months to 34.3 months	1-year risk of progression[b]		HR 1.01 (0.85 to 1.19)	900 (6 RCTs)	⊕⊕⊕⊝ MODERATE[c]	
	880 per 1000	883 per 1000 (835 to 920)				
Objective response rate follow-up range: 1.5 months to 18 months	318 per 1000	309 per 1000 (268 to 354)	RR 0.97 (0.84 to 1.11)	4200 (12 RCTs)	⊕⊕⊕⊝ MODERATE[c]	
Quality of life assessed with: EORTC QLQ-C30 or Rotterdam Symptom Checklist assessed at baseline and at 2 years (or later)	Not estimable. In general, there did not seem to be differences in global health scores between the 2 treatment groups at around 2 years' follow-up		-	(5 RCTs)	⊕⊕⊝⊝ LOW[d]	Most studies used the validated EORTC QLQ-C30 questionnaire (4 studies) or the Rotterdam Symptom Checklist (1 study), and measures were patient-reported

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer core quality of life questionnaire; HR:**h**azard ratio; ORR: objective response rate; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Baseline risk in the comparator arm was based on 1-year estimates from 11 studies for OS (BOLERO6; Chan 2009; CHAT; Fan 2013; IMELDA; METRIC; Pallis 2012; Seidman 2011; SO140999; Study 301; TURANDOT), as well as on data from a subset of studies that reported the event rate at 1 year in the comparator arm based on hormone receptor status (i.e. hormone receptor-positive: BOLERO6; IMELDA; SO140999; hormone receptor-negative: IMELDA; METRIC; SO140999).

[b]Baseline risk in the comparator arm was based on 1-year estimates from all 12 studies that reported on PFS, as well as on data from one study for hormone receptor status (i.e. hormone receptor-positive: BOLERO6; hormone receptor-negative: METRIC).

[c]Studies were open-label with limited independent assessment/central review of these outcomes. We thought some bias may be introduced by lack of blinding when PFS and ORR were assessed; therefore we downgraded the certainty of evidence by one level for risk of bias.

[d]This outcome was downgraded because all measures were patient-reported, taking place in open-label studies, and therefore was at high risk of bias. Although most studies used the validated EORTC QLQ-C30 questionnaire; there was also variability in time frames when women were given the questionnaires and different lengths of follow-up.

Summary of findings 2. Capecitabine-containing regimens compared to non-capecitabine-containing regimens for neoadjuvant treatment

Capecitabine-containing regimens compared to non-capecitabine-containing for neoadjuvant treatment of ER-positive versus ER-negative breast cancer

Patient or population: neoadjuvant treatment of ER-positive vs ER-negative breast cancer
Setting: outpatient
Intervention: capecitabine-containing regimens
Comparison: regimens without capecitabine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with non-capecitabine-containing regimens	Risk with capecitabine-containing regimens				
Pathological complete response (pCR): breast and axillary nodes follow-up: range 3 months to 9 months	202 per 1000	221 per 1000 (193 to 252)	OR 1.12 (0.94 to 1.33)	3152 (6 RCTs)	⊕⊕⊕⊕ HIGH	No serious concerns, although it is noted that Yoo 2015 was deemed to be at high risk of selection bias
pCR: hormone receptor-positive follow-up: range 3 months to 9 months	54 per 1000[a]	65 per 1000 (42 to 101)	OR 1.22 (0.76 to 1.95)	964 (4 RCTs)	⊕⊕⊕⊝ MODERATE[b]	
pCR: hormone receptor-negative follow-up: range 3 months to 9 months	179 per 1000[a]	219 per 1000 (118 to 368)	OR 1.28 (0.61 to 2.66)	646 (4 RCTs)	⊕⊕⊕⊝ MODERATE	
Disease-free survival median follow-up: range 3 years to 5.4 years	5-year risk of recurrence		HR 1.02 (0.86 to 1.21)	2499 (4 RCTs)	⊕⊕⊕⊕ HIGH	
	249 per 1000[c]	253 per 1000 (218 to 292)				
Overall survival median follow-up: range 3 years to 5.4 years	5-year risk of death		HR 0.97 (0.77 to 1.23)	2499 (4 RCTs)	⊕⊕⊕⊕ HIGH	
	164 per 1000[c]	160 per 1000 (129 to 198)				
Febrile neutropenia	66 per 1000	85 per 1000	OR 1.31	2890	⊕⊕⊕⊝	

follow-up: range 3 months to 9 months		(64 to 112)	(0.97 to 1.77)	(4 RCTs)	MODERATE[d]
Diarrhoea follow-up: range 3 months to 9 months	38 per 1000	72 per 1000 (50 to 104)	OR 1.95 (1.32 to 2.89)	2686 (3 RCTs)	⊕⊕⊕⊝ MODERATE[d]
Hand-foot syndrome follow-up: range 3 months to 9 months	31 per 1000	179 per 1000 (136 to 232)	OR 6.77 (4.89 to 9.38)	3021 (5 RCTs)	⊕⊕⊕⊝ MODERATE[d]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; ER: oestrogen receptor; HR: hazard ratio; OR: odds ratio; RCT: randomised controlled trial.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Baseline risk in the control arm was based on three studies (Lee 2008; Yoo 2015; Zhang 2016), which reported on hormone receptor-positive and hormone receptor-negative data separately.
[b]Downgraded by 1/2 point due to imprecision (confidence intervals include no effect; appreciable benefit and harm) and by an additional 1/2 point for reporting bias (neither of the two largest studies reported pCR by hormone receptor status).
[c]Baseline risk in the control arm was based on 5-year estimates from two studies (GeparQuattro; NSABP-40).
[d]Downgraded by 1/2 point due to imprecision (wide confidence intervals) and by 1/2 point for risk of detection bias because all studies were open-label, and toxicity assessment (by assessor or patient) may be influenced by lack of blinding of treatment arm.

Summary of findings 3. Capecitabine-containing regimens compared to non-capecitabine-containing regimens or no chemotherapy for early breast cancer

Capecitabine-containing regimens compared to non-capecitabine-containing regimens or no chemotherapy for ER-positive vs ER-negative breast cancer

Patient or population: people with early breast cancer
Setting: outpatient
Intervention: capecitabine-containing regimens
Comparison: non-capecitabine-containing regimens or no chemotherapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with non-capecitabine-con-	Risk with capecitabine-containing regimens			

	taining regimens or no chemotherapy				
Disease-free survival (DFS) median follow-up: range 3.6 years to 10.3 years	5-year risk of recurrence[a]		HR 0.93 (0.86 to 1.01)	13547 (8 RCTs)	⊕⊕⊕⊝ MODERATE[b]
	166 per 1000	155 per 1000 (145 to 168)			
DFS: hormone receptor-positive median follow-up: range 3.6 years to 10.3 years	5-year risk of recurrence[a]		HR 1.03 (0.91 to 1.17)	5604 (5 RCTs)	⊕⊕⊕⊝ MODERATE[b]
	289 per 1000	296 per 1000 (267 to 329)			
DFS: hormone receptor-negative median follow-up: range 3.6 years to 10.3 years	5-year risk of recurrence[a]		HR 0.76 (0.65 to 0.88)	2879 (7 RCTs)	⊕⊕⊕⊝ MODERATE[b]
	429 per 1000	347 per 1000 (305 to 389)			
Overall survival (OS) median follow-up: range 3.6 years to 10.3 years	5-year risk of death[c]		HR 0.89 (0.81 to 0.98)	13547 (8 RCTs)	⊕⊕⊕⊕ MODERATE[b]
	104 per 1000	93 per 1000 (85 to 102)			
Febrile neutropenia follow-up: range 4 months to 24 months	109 per 1000	63 per 1000 (54 to 73)	OR 0.55 (0.47 to 0.64)	8086 (5 RCTs)	⊕⊕⊕⊝ MODERATE[d]
Diarrhoea follow-up: range 4 months to 24 months	25 per 1000	59 per 1000 (48 to 71)	OR 2.46 (2.01 to 3.01)	11207 (8 RCTs)	⊕⊕⊕⊝ MODERATE[d]
Hand-foot syndrome follow-up: range 4 months to 24 months	13 per 1000	139 per 1000 (112 to 171)	OR 13.60 (10.65 to 17.37)	11207 (8 RCTs)	⊕⊕⊕⊝ MODERATE[d]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; ER: oestrogen receptor; HR: hazard ratio; OR: odds ratio; RCT: randomised controlled trial; RFS: recurrence-free survival.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Baseline risk in the control arm was based on 5-year estimates from seven studies for DFS/RFS (CBCSG-10; CIBOMA 2004-01; CREATE-X; FINXX; GEICAM 2003-10; ICE; USON 01062), and data from the Oxford overview on women ≥ 50 years of age with ER-positive breast cancer (Figure 5 in EBCTCG 2005) and < 50 years of with ER-poor breast cancer (Figure 5 in EBCTCG 2005) for DFS hormone receptor-positive and hormone receptor-negative breast cancer, respectively.

[b]Downgraded by 1/2 point due to some concerns related to attrition bias in three studies and by 1/2 point for indirectness due to inclusion in some studies of people with worse prognosis than in other studies.

[c]Baseline risk in the control arm was based on 5-year estimates from seven studies (CBCSG-10; CIBOMA 2004-01; FINXX; GEICAM 2003-10; ICE; TACT2; USON 01062).

[d]Downgraded by 1/2 point due to inconsistency (substantial heterogeneity; confidence intervals do not overlap in the case of febrile neutropenia or diarrhoea) and by 1/2 point for risk of detection bias because all studies were open-label and toxicity assessment (by assessor or patient) may be influenced by lack of blinding of treatment arm.

BACKGROUND

Description of the condition

Breast cancer is the most common malignancy among women in the world, with an estimated 2.1 million new cases diagnosed in 2018, accounting for 24% of all cancers in women (Bray 2018). Breast cancer is the fifth leading cause of cancer-related death worldwide. In more developed regions, it is the second leading cause of cancer-related mortality among women, and it is the leading cause in less-developed regions (Ferlay 2012).

Five-year survival following a diagnosis of breast cancer has significantly increased over the past 20 years. This is due in part to the implementation of population screening resulting in diagnosis of breast cancer at earlier stages and in part to improvements in adjuvant systemic treatment. The development and availability of additional endocrine therapies (EBCTCG 2005), human epidermal growth factor receptor 2 (HER2)-targeted agents (Moja 2012), and new chemotherapeutic drug classes, such as taxanes (Ferguson 2007), have contributed significantly to better outcomes. The expansion of available cytotoxic agents, including capecitabine, vinorelbine, and eribulin, has also coincided with improved survival for women with metastatic breast cancer, although trials confirming survival advantages are relatively scarce due to the allowance of cross-over within many trial designs. Evidence guiding the use of endocrine and HER2-targeted therapies is well defined. In contrast, despite evidence for a substantial difference in overall chemotherapy sensitivity between endocrine responsive and non-responsive breast cancers, as judged by pathological complete response (pCR) rates in the neoadjuvant setting (Houssami 2012), there is a paucity of data guiding the selection of chemotherapeutic agents with respect to hormone receptor status or other tumour features. Such guidance is particularly important in triple-negative breast cancer (TNBC), which carries the poorest prognosis of all breast cancer subtypes, and when chemotherapy is the only option for systemic treatment. In the adjuvant setting, optimising the treatment regimen should improve cure rates. Platinum-based compounds have been investigated for adjuvant treatment of TNBC, but results are conflicting, with generally improved pCR rates not translating into consistent survival advantages (Gerratana 2016). Capecitabine is an alternative agent that has been investigated. It is generally well tolerated, lacks cross-resistance with other adjuvant agents due to a different mechanism of action, and is readily integrated into existing standard treatments. However, data regarding the efficacy of capecitabine-containing chemotherapy regimens compared to similar non-capecitabine-containing regimens according to cancer subtype, including TNBC, are fragmented. As such, optimal selection of chemotherapy in breast cancer within the oestrogen-driven, HER2, and TNBC subgroups remains to be defined.

Description of the intervention

Capecitabine is an oral pro-drug of fluorouracil. Following absorption, capecitabine is metabolised in the normal liver and in cancerous tissue. The final step in the conversion of capecitabine to fluorouracil is catalysed by thymidine phosphorylase, which is highly expressed in many cancer cells (Miwa 1998). As such, the effect of capecitabine is concentrated within these cells, giving a selective treatment advantage. Capecitabine has been used extensively as a single agent and more occasionally as part of combination regimens for metastatic breast cancer. Its use as a component of adjuvant and neoadjuvant therapy for breast cancer has been investigated in clinical trials.

Adverse effects commonly reported in association with capecitabine, experienced by 5% or more of patients, include diarrhoea, stomatitis, nausea and vomiting, hand-foot syndrome (palmar-plantar erythrodysaesthesia), dermatitis, fatigue, and cytopenia. Coronary artery vasospasm is a less common but clinically important side effect that is reported to affect 0.2% of patients (FDA 2014).

How the intervention might work

A pooled analysis of individual patient data from capecitabine monotherapy trials for locally advanced or metastatic disease demonstrated that patients with hormone receptor-positive breast cancer experienced significantly higher overall response rates, progression-free survival, and overall survival compared with patients with hormone receptor-negative disease (Blum 2012). Several retrospective reviews have identified significantly greater benefits from capecitabine in hormone receptor-positive metastatic breast cancer (Gluck 2009; Osako 2009; Siva 2008). However, when both overall response rate (ORR) and overall survival (OS) are interpreted in the context of metastatic disease, it is important to take into account the observations that hormone receptor-negative disease natively tends to have a higher ORR than chemotherapy (particularly anthracyclines and taxanes), whereas hormone receptor-positive disease is known to carry a longer median OS, regardless of the treatment parameters.

In the neoadjuvant setting, capecitabine-containing chemotherapy regimens have been associated with greater benefit for hormone receptor-positive breast cancer. In an unplanned subgroup analysis from the large phase 3 GeparTrio trial, investigating a response-guided treatment switch to capecitabine-vinorelbine after poor response to two initial cycles of docetaxel - doxorubicin and cyclophosphamide - patients with hormone receptor-positive breast cancers experienced significantly longer disease-free survival with the capecitabine combination compared to their hormone receptor-negative counterparts (von Minckwitz 2008). A second phase 3 trial examining the use of neoadjuvant docetaxel-capecitabine (TX) versus doxorubicin-cyclophosphamide (AC) found that TX was associated with a higher rate of pathological complete response, at 17% in hormone receptor-positive breast cancers, compared with 3% for AC (Lee 2008).

Why it is important to do this review

In the adjuvant setting, anthracyclines and taxanes form the backbone of treatment regimens. This remains the optimal treatment scenario in which the plethora of newer agents could contribute further to cure rates. However, their potential incorporation has been hampered by trials with large numbers of low-risk patients, heterogenous patient populations, and diverse designs. The division of breast cancers into oestrogen receptor-positive (ER+) versus oestrogen receptor-negative (ER-) tumours represents the most fundamental biological classification. This concept, combined with the above evidence for a dichotomous effect between the two groups, has led us to investigate whether collation of existing capecitabine trial outcome data by hormone receptor status could reveal a group significantly advantaged by routine incorporation of the drug in adjuvant or neoadjuvant therapy, thereby guiding the selection of chemotherapy.

In metastatic breast cancer, ideally patients would receive the majority of active agents at some time during their disease course. However, data from Australia and from a large insured cohort in the USA show that less than half of patients are treated beyond a second line of therapy, making selection of the most effective agents for early-line treatments crucial (Martin 2015; Ray 2013).

When data are insufficient to define optimal subtype-specific treatment pathways, this review may guide the development of randomised trials in more targeted populations. Finally, findings from this study may inform a review of regulations regarding the funding of capecitabine in various settings.

OBJECTIVES

To assess effects of chemotherapy regimens containing capecitabine compared with regimens not containing capecitabine for women with hormone receptor-positive versus hormone receptor-negative breast cancer across the three major treatment scenarios: neoadjuvant, adjuvant, metastatic.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) comparing chemotherapy regimens containing capecitabine alone or in combination versus a control employing a similar regimen without capecitabine for treatment of breast cancer were included. Randomised studies that included a capecitabine-containing regimen but did not directly compare this against a non-capecitabine-containing regimen as the primary trial endpoint were also included. Additionally, trials in which a capecitabine-containing regimen was part of a "pooled comparator" or was included as "physician's choice" were included, as long as capecitabine outcomes were reported. Full-text review was performed when available, and data were extracted by ER, hormone receptor, or TNBC status, if provided.

We anticipated that we would identify three or more RCTs for each section of this review. However, if we identified fewer than three RCTs for any of the three sections of this review, we would consider well-designed non-randomised controlled trials.

Types of participants

Trials studying women with a histological diagnosis of breast adenocarcinoma were included. Treatment could be provided at any stage (adjuvant, neoadjuvant, or metastatic) and for any line of treatment in the metastatic setting. We applied no age restrictions. Only studies in which at least 75% of participants had a defined hormone receptor status were eligible.

Types of interventions

- Intervention: chemotherapy regimens containing capecitabine alone or as part of combination therapy in hormone receptor-positive and hormone receptor-negative breast cancer (Table 1)
- Comparator: similar chemotherapy regimens not containing capecitabine in hormone receptor-positive and hormone receptor-negative breast cancer. The comparator could include:
  - the same chemotherapy regimen without capecitabine;
  - a different chemotherapy regimen without capecitabine;
  - the same chemotherapy regimen with another drug or drugs substituting for capecitabine; or
  - no active agents in the adjuvant setting (Table 1).

Comparisons included:

- capecitabine-containing regimen versus non-capecitabine-containing regimen in hormone receptor-positive breast cancer;
- capecitabine-containing regimen versus non-capecitabine-containing regimen in hormone receptor-negative breast cancer; and
- capecitabine-containing regimen versus non-capecitabine-containing regimen in TNBC.

We also included studies in which the strategy was:

- chemotherapy given as neoadjuvant, adjuvant, or palliative treatment;
- inclusive of biologic agents such as trastuzumab and bevacizumab, if relevant, and provided identical biologics are included in capecitabine-containing and non-capecitabine-containing arms; or
- chemotherapy given as first or subsequent line of treatment in the context of metastatic disease.

Types of outcome measures

Primary outcomes

Palliative chemotherapy

- Overall survival (OS)

Neoadjuvant chemotherapy

- Pathological complete response rate (pCR)

Adjuvant chemotherapy

- Overall survival (OS)

Secondary outcomes

Palliative chemotherapy

- Overall response rate (ORR)
- Progression-free survival (PFS)
- Clinical benefit rate (CBR)
- Quality of life (QoL)

Neoadjuvant chemotherapy

- Disease-free survival (DFS)
- Recurrence-free survival (RFS)
- Overall survival (OS)

Adjuvant chemotherapy

- Disease-free survival (DFS)
- Recurrence-free survival (RFS)

Specific information on adverse events was collected from studies in each of the neoadjuvant, adjuvant, and palliative chemotherapy groups. The total number of grade 3 and 4 adverse events and the total number of participants at risk in each trial were summated to calculate a single odds ratio. For the following specific toxicities of interest, the total number of toxic events was calculated.

- Cytopenias.
- Febrile neutropenia.
- Hand-foot syndrome.
- Mucositis and stomatitis.
- Diarrhoea.
- Ischaemic cardiac disease.

The following outcome definitions were applied.

- pCR defined in Measures of treatment effect section.
- DFS defined as time from randomisation to time of identification of recurrent or metastatic cancer or death from any cause.
- RFS defined as time from randomisation to date of diagnosis of invasive breast cancer recurrence or death if the patient died before cancer recurrence.
- PFS defined as time from randomisation to time of tumour progression or death from any cause. If time to progression or time to treatment failure was recorded as an endpoint rather than PFS, these could be used in place of PFS.
- OS defined as time from randomisation to death from any cause.
- Breast cancer-specific survival (BCSS) defined as time from randomisation to death due to breast cancer.
- Response rate defined by Response Evaluation Criteria In Solid Tumours (RECIST) (Eisenhauer 2009).
- ORR defined as the sum of complete and partial responses, representing the best response for each patient.
- CBR defined as the sum of complete response, partial response, and stable disease rate.

Search methods for identification of studies

Electronic searches

Details of search strategies used by the Cochrane Breast Cancer Group (CBCG) for identification of studies and the procedure used to code references are outlined in the Group's module (http://www.mrw.interscience.wiley.com/cochrane/clabout/articles/BREASTCA/frame.html). Trials with the key words 'breast neoplasm; breast cancer; breast carcinoma; breast adenocarcinoma; breast tumour/tumor; capecitabine; and xeloda' were extracted and considered for inclusion in the review. We searched the following databases.

- CBCG Specialised Register (4 June 2019).
- MEDLINE Ovid (1946 to 4 June 2019; see Appendix 1).
- Embase Ovid (1974 to 4 June 2019; see Appendix 2).
- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library (searched 4 June 2019; see Appendix 3).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/trialsearch/Default.aspx; searched 4 June 2019; see Appendix 4).
- Clinicaltrials.gov (http://clinicaltrials.gov/; searched 4 June 2019; see Appendix 5).

Searching other resources

Bibliographic searching

We identified further studies from the reference lists of relevant trials or reviews identified above. We obtained a copy of the full article for each reference reporting a potentially eligible trial. When this was not possible, we attempted to contact study authors to request additional information.

Grey literature searching

We searched conference proceedings of the following conferences from 1996 to the present for relevant abstracts.

- American Society of Clinical Oncology Annual Scientific Meeting.
- San Antonio Breast Cancer Symposium.
- American Society of Clinical Oncology Breast Cancer Symposium.
- European Society of Medical Oncology Annual Scientific Meeting.
- European Breast Cancer Conference.

Data collection and analysis

Selection of studies

We applied the selection criteria to each reference identified independently by two review authors (of PL, AW, SH, PB, AR). We linked records identified at the initial screening stage to studies at the full-text screening stage.

With regard to selection of studies,

- review authors were not blinded to study title, authors, or publication details;
- any disagreements regarding selection of a study were resolved by a third review author (AR or MB, unless AR was an initial assessor);
- PL, AW, SH, and PB are not content experts, although all are knowledgeable in the field;
- AR is a content expert, and MB is an expert in statistics;
- all relevant studies were included (no studies required translation); and
- we recorded significant excluded studies in the Characteristics of excluded studies table (references were not included in this table if they obviously did not fulfil the inclusion criteria).

Data extraction and management

Two review authors (of PL, AW, SH, PB, AR) independently extracted data from each publication or abstract.

We performed data extraction by using standard electronic extraction forms (see Appendix 6) and entered the data into Covidence (http://www.covidence.org). We designed individual data extraction forms for each of the three treatment types studied: neoadjuvant, adjuvant, and palliative treatment. When data from trials were presented in multiple publications, we amalgamated the information and reported it as a single trial, with all relevant publications listed.

Disagreements regarding extraction of quantitative data were resolved by a third review author (AR or PL).

Assessment of risk of bias in included studies

We assessed risk of bias by using Cochrane's risk of bias assessment tool, provided in the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 8.5 (Higgins 2011). Two review authors (of PL, AW, SH, PB, AR) independently assessed risk of bias, with disagreements resolved by a third review author (AR or PL). Areas of bias assessed were:

- selection bias;
- performance bias;
- detection bias;
- attrition bias;
- reporting bias; and
- other biases;
  - recruitment bias - recruitment based on differential response; and
  - use of interim results.

We described risk of bias assessments in a 'Risk of bias' table (see Characteristics of included studies table), and we presented summary graphs for palliative, neoadjuvant, and adjuvant trials.

Measures of treatment effect

Palliative trials

The primary outcome for palliative intent trials was OS, which was analysed as a time-to-event outcome and was expressed as a hazard ratio (HR). We used the HR provided in each study or estimated the HR indirectly by using the methods described by Tierney et al and Parmar as above, and we documented this information as above. For meta-analytical pooling, we used the generic-inverse variance method as described in the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapters 7.7.6 and 9.4.9, as for other outcomes.

Secondary outcomes for palliative intent trials were overall response rate (ORR), progression-free survival (PFS), and clinical benefit rate (CBR). ORR is considered a small ordinal scale that was expressed as a dichotomous outcome, with complete response (CR) and partial response (PR) representing response, and stable disease (SD) and progressive disease (PD) representing no response. This outcome has been presented as a risk ratio (RR) with 95% confidence interval (CI) and has been reported for randomised and assessable patients. We have reported the ratio of treatment effect for response, so that an RR less than 1.0 favours non-capecitabine-containing regimens and a RR equal to or greater than 1.0 favours capecitabine-containing regimens. CBR was also considered a small ordinal scale and was expressed as a dichotomous outcome, with CR, PR, and SD (for three months or longer) representing clinical benefit, and PD representing no benefit. We presented the outcome as an RR with 95% CI, as per the ORR above. We analysed PFS as a time-to-event outcome, also as above.

When both ORR and OS are interpreted in the context of metastatic disease, it is important to take into account that hormone receptor-negative disease natively tends to have a higher ORR than chemotherapy, whereas hormone receptor-positive disease is known to carry a longer median OS, regardless of the treatment parameters. In this setting, an absolute 10% or greater improvement in ORR in hormone receptor-positive disease for capecitabine-containing regimens compared with non-capecitabine-containing regimens was considered a clinically significant difference.

Neoadjuvant trials

The primary outcome for neoadjuvant trials was the pathological complete response rate (pCR). In most trials, this was measured on the Modified Regression Scale (von Minckwitz 2008), with response graded as follows.

- Grade 5 - no microscopic evidence of residual tumour cells in the breast or axillary nodes.
- Grade 4 - no microscopic evidence of residual tumour cells in the breast, but axillary nodes involved.
- Grade 3 - residual non-invasive tumour cells in the breast.
- Grade 2 - residual focal invasive tumour cells in the breast ≤ 5 mm.
- Grade 0 to 1 - all remaining scenarios including the presence of new invasive tumour.

Grades 4 and 5 were considered to represent pCR. This is a small ordinal scale on which the event of pCR was considered as a dichotomous outcome with grades 4 and 5 representing pCR, and all other grades representing no pCR. This outcome has been presented as a risk ratio (RR) with 95% confidence interval (CI) and has been reported for randomised and assessable patients. We reported the ratio of treatment effect for response, so that an RR less than 1.0 favours non-capecitabine-containing regimens and an RR equal to or greater than 1.0 favours capecitabine-containing regimens. In the context of neoadjuvant treatment, pCR rates are typically significantly higher in hormone receptor-negative cancers relative to hormone receptor-positive cancers. Thus, in hormone receptor-positive disease, an absolute difference of 5% or greater for capecitabine-containing regimens compared with non-capecitabine-containing regimens was considered a clinically significant difference.

Secondary outcomes for neoadjuvant trials were disease-free survival (DFS), recurrence-free survival (RFS), and overall survival (OS). These have been analysed as time-to-event outcomes and expressed as hazard ratios (HRs). We used the HR provided in each study or estimated the HR indirectly using methods described by Tierney and Parmar (Parmar 1998; Tierney 2007). We recorded the use of indirect methods in the Notes sections of the Characteristics of included studies table. For meta-analytical pooling, we employed the generic-inverse variance method as described in the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapters 7.7.6 and 9.4.9 (Higgins 2011).

Adjuvant trials

The primary outcome for adjuvant trials was overall survival (OS), which was analysed as a time-to-event outcome and was expressed as an HR. We used the HR reported in each study or estimated the HR indirectly, again using methods described by Tierney and Parmar (Parmar 1998; Tierney 2007). Similarly, for meta-analytical pooling, we used the generic-inverse variance method as described in the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapters 7.7.6 and 9.4.9.

Secondary outcomes for adjuvant trials were DFS, RFS, and breast cancer-specific survival (BCSS). We analysed these as time-to-event outcomes and expressed them as HRs. We used the HR provided in each trial publication or estimated the HR indirectly using methods described by Tierney and Parmar, as above, and we will document this as above. Again, for meta-analytical pooling, we used the generic-inverse variance method as described above.

In the adjuvant setting, an absolute improvement of 5% or greater in DFS, RFS, and OS for capecitabine-containing regimens compared with non-capecitabine-containing regimens was considered a clinically significant difference for hormone receptor-positive disease.

Adverse events

All grade 3 and 4 adverse events, along with the total number of participants at risk, were recorded from each trial. When possible, data on adverse events were collected for the treated population rather than for the intention-to-treat population. A pooled odds ratio (OR) with 95% CI was calculated for each toxicity that was reported in two or more studies. Total numbers of the following specific adverse events were recorded in this review: cytopenias, febrile neutropenia, hand-foot syndrome, mucositis, diarrhoea, and ischaemic cardiac disease.

Unit of analysis issues

We did not include cross-over trials in this systematic review. Exceptions to this criterion were made if a trial detailed outcome data for capecitabine-containing chemotherapy regimens that were not affected by cross-over. For example, ORR and PFS in metastatic trials are outcomes that are not intuitively affected by cross-over; thus we included such trials if data were available for full-text review. In contrast, OS differences might be expected to be attenuated by cross-over and so were not included.

Some included studies contained multiple intervention groups. The review author MB provided specialist statistical advice regarding the manner in which multiple intervention groups were dealt with. Each study utilising multiple groups was considered independently and multiple groups were handled in various ways, including by combining intervention groups or dividing the control group, as deemed appropriate to enable pair-wise comparisons and to ensure that no unit of analysis issues arose.

Dealing with missing data

In planning this systematic review, we considered missing data to be of likely significance, as we anticipated that many of the studies meeting eligibility criteria for inclusion would not report outcomes based on the tumour hormone receptor status of participants. For such cases, this meant that analysis of the study for inclusion in the systematic review was not possible.

We did not contact the original investigators regarding missing hormone receptor status data of participants. Studies for which this information was not available have been included in the review, and we have discussed the impact of the missing data for these studies in the Discussion section of the review.

With regard to studies in which other data are missing, for example, participants lost to follow-up or data for study objectives were not reported:

- analysis has been done by intention-to-treat, with a sensitivity analysis conducted to consider the impact of the missing results;
- missing data have not been imputed; and
- the impact of missing data with regard to assessment of bias has been discussed in the Discussion section of the review.

Assessment of heterogeneity

We assessed statistical heterogeneity by using:

- visual inspection of forest plots;
- the chi^2 test, with a cut-off point of $P = 0.1$; and
- the I^2 statistic (heterogeneity was considered if I^2 value exceeded 50%).

We used a random-effects model to address heterogeneity, depending on evidence of statistical heterogeneity, and we identified potential sources of heterogeneity.

We carried out pre-planned comparative analyses of outcomes by hormone receptor status, as heterogeny by this tumour demographic parameter was the core topic of the review. Although heterogeny was seen for outcomes in all three scenarios, this disappeared in the adjuvant setting when analysis was performed by hormone receptor status, but not in metastatic or neoadjuvant settings.

Additionally, as relevant studies were compiled, it became apparent in both adjuvant and metastatic scenarios that the manner of capecitabine incorporation varied. In the metastatic setting, this could be done by adding capecitabine to an existing regimen, substituting for a component of an existing regimen, or using monotherapy. In the adjuvant setting, capecitabine could be added immediately after surgery as part of standard fully adjuvant treatment, or it could be added sequentially following (neo)adjuvant chemotherapy. Analyses by trial incorporation type were consequently carried out with the goal of assessing impact on heterogeny, and because choice of incorporation method is a pertinent clinical question that the clinician is required to answer when applying trial findings.

When we encountered heterogeny that was unexplained by the above sources, we considered further potential clinical factors, including differences in comparator cytotoxic drugs, racial origins of patient populations, drug dosages and schedules, and disease stage.

Assessment of reporting biases

Testing for funnel plot asymmetry in this review was limited by the number of studies included for each of the primary outcome measures, as we identified fewer than 10 studies for two of the three arms of this review. However, in the metastatic arm, the number of studies was sufficient, and so funnel plot asymmetry was tested according to the methods listed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 10.4.3), and this was overseen by our statistician (MB).

In some instances, publication bias may not lead to asymmetry in the funnel plot. Furthermore, visual inspection of the funnel plot for asymmetry alone is subjective and may lead to failure to detect publication bias. Thus, funnel plot asymmetry is limited with respect to determination of publication bias. Funnel plot asymmetry may also be caused by:

- differences in methodological quality between studies;

- true heterogeneity between studies; or
- chance.

Funnel plots were used only in the metastatic setting to detect publication bias. When possible, we reviewed the protocols of included studies in all three settings to assess outcome reporting bias. When additional studies were available from review updates, we assessed publication or other bias by visually examining funnel plot symmetry in neoadjuvant and adjuvant settings, provided at least 10 studies were available for examination in each area.

In the metastatic setting, we created funnel plots for OS, PFS, and ORR. In our plots, there were no points in the second half of the plot, which may indicate publication bias; however small and large sample sizes did not yield different results, and studies were few. Supplementary to visual inspection of the funnel plot, we conducted Egger's test for OS, PFS, and ORR, using R (metaphor package; R). We found no significant results.

- OS: t = -0.7601, df = 10, P = 0.4647.
- PFS: t = 1.2136, df = 10, P = 0.2528.
- ORR: t = -0.3509, df = 10, P = 0.7330.

Other possible sources of publication bias considered include duplicate or multiple publication bias, location bias, citation bias, language bias, and outcome reporting bias, all of which could have affected this review. We endeavoured to detect duplicate or multiple publications of the same study, although we appreciated the difficulties involved in doing this. We searched numerous electronic databases, including those of trial registries and those citing grey literature, to minimise location biases. We did not limit our inclusion criteria by language.

Data synthesis

We pooled dichotomous outcomes by using the Mantel-Haenszel fixed-effect model method. We pooled time-to-event outcomes by using the generic inverse-variance method, allowing a mixture of log-rank and Cox model estimates to be obtained from these studies. We used RevMan version 5.32 software to perform the analysis.

When no events are observed in one or both groups in an individual study, computational problems can occur when relative effect measures (such as odds ratios) are calculated by Mantel-Haenszel methods. To deal with this, RevMan automatically adds 0.5 to all cells if the same cell is zero in all included studies (see *Cochrane Handbook for Systematic Reviews of Interventions*, version 5, Chapter 16). RevMan excludes studies from the meta-analysis when there are no events in both arms, because such studies do not provide any indication of the direction or magnitude of the relative effect (see *Cochrane Handbook for Systematic Reviews of Interventions*, version 5, Chapter 16).

Subgroup analysis and investigation of heterogeneity

Some of the pre-planned subgroup assessments as outlined in the protocol were not performed. Details of this are discussed in the section Differences between protocol and review.

We presented data separately for participants receiving neoadjuvant, adjuvant, and palliative chemotherapy. We also presented data separately for the following pre-specified patient subgroups.

- Hormone receptor-positive disease.
- Hormone receptor-negative disease.
- Triple-negative disease.

As previously discussed, after identifying studies that could be categorised by method of capecitabine incorporation, we performed subgroup analyses by study design for all patients and for all hormone receptor subgroups.

Sensitivity analysis

We performed sensitivity analysis to assess the robustness of results. Due to imbalanced reporting of DFS and RFS, we combined these outcomes and performed a sensitivity analysis to ensure that there was not a significant difference due to this. Additionally, in the metastatic setting, we included a pooled analysis (Seidman 2014; pooled analysis of Chan 2009 and Seidman 2011), as primary outcome data by hormone receptor status were not reported individually. We performed a sensitivity analysis to assess the impact of Seidman 2014. We acknowledge this to be a source of potential bias in the review process. We initially considered a second pooled analysis for inclusion (Pivot 2016; pooled analysis of EMBRACE and Study 301), but subsequently, outcome data by hormone receptor status for Study 301 were published, and we deemed that, given (1) uncertainty in the heterogeneity of pooled effect estimates, (2) undue weighting of pooled effect estimates, and (3) the small number of patients that EMBRACE contributed to the overall number of patients in the pooled analysis (44 patients from EMBRACE, out of a total of 698 in the pooled analysis), it would pose less of a risk of potential bias to exclude both EMBRACE and Pivot 2016.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach to assess the certainty of evidence and GRADEproGDT software to develop the 'Summary of findings' table, in accordance with GRADE guidance (GRADEproGDT; Schünemann 2019). Two review authors (TB, MW) graded the certainty of evidence for this review update.

Key outcomes for palliative chemotherapy were overall survival, progression-free survival, objective response rate, and quality of life; for neoadjuvant chemotherapy pCR, disease-free survival, overall survival, febrile neutropenia, diarrhoea, and hand-foot syndrome; and for adjuvant chemotherapy disease-free survival, overall survival, febrile neutropenia, diarrhoea, and hand-foot syndrome.

To calculate absolute risk of the comparator group for time-to-event outcomes, we estimated the event rate at specific time points (i.e. palliative chemotherapy: one year for overall survival and progression-free survival; neoadjuvant chemotherapy: five years for disease-free survival and overall survival; adjuvant chemotherapy: disease-free survival and overall survival) from the Kaplan-Meier curves or reported event rates. We entered these estimated values into GRADEproGDT, and corresponding absolute risks for the intervention group at one or five years were automatically populated by GRADEproGDT.

RESULTS

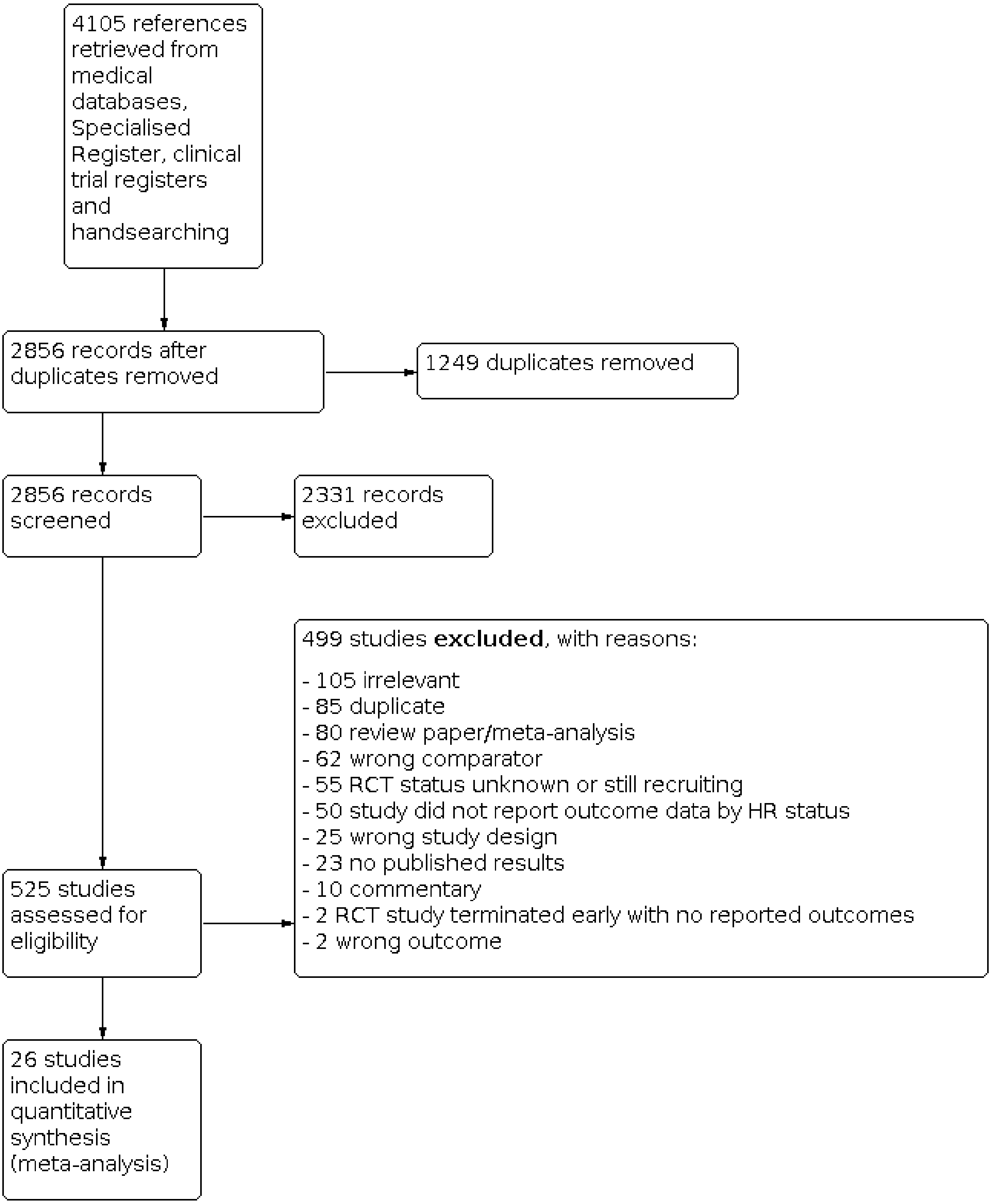
Description of studies

See Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; and Characteristics of ongoing studies.

Results of the search

The capecitabine-related terms outlined in the search strategy yielded 4105 records through medical databases, the Specialised Register, clinical trial registers, and handsearching (see Figure 1). Following duplicate exclusion and initial screening, 525 records remained for full-text review. A further 498 references initially deemed potentially eligible were excluded; the most common reasons for exclusion were irrelevance to the review question (105), representing a review or meta-analysis (80), involving a wrong comparator (62), and having inadequate outcome data reported by hormone receptor status (50), leaving 26 suitable studies for inclusion in the review.

Figure 1. PRISMA study flow diagram.



Included studies

See Characteristics of included studies and Table 1, which outline the treatment regimens across studies.

A total of 26 RCTs evaluated the efficacy of capecitabine in breast cancer, with available outcome data stratified by hormone receptor status, ER status, or TNBC status. Metastatic RCTs (n = 12) included SO140999, TURANDOT, Study 301, CHAT, Fan 2013, Pallis 2012, TABEA, IMELDA, BOLERO6, METRIC, Chan 2009, Seidman 2011, and

Seidman 2014 (pooled analysis of Chan 2009 and Seidman 2011). The six neoadjuvant RCTs included were NSABP-40, ABCSG-24, GeparQuattro, Lee 2008, Zhang 2016, and Yoo 2015. The eight adjuvant studies that provided data by hormone receptor or TNBC status were USON 01062, FINXX, GEICAM 2003-10, ICE, CBCSG-10, CIBOMA 2004-01, TACT2, and CREATE-X.

All metastatic trials except one - METRIC - have been published in peer-reviewed journals. The overall number of patients ranged from 53 in Fan 2013 (single centre, phase 2) to 1102 in Study 301 (169 sites, phase 3). Median follow-up of trials varied from 18.6 months in TURANDOT to 37.6 months in BOLERO6. Although the proportion of patients with unknown hormone receptor status exceeded our threshold of 25% in SO140999, this study was nevertheless included based on the details of available data. Both Seidman 2011 and Chan 2009 compared docetaxel-gemcitabine versus docetaxel-capecitabine. The dose of capecitabine was higher in Chan 2009 (1250 mg/m^2 twice daily) than in Seidman 2011 (1000 mg/m^2 twice daily), but schedules were identical in all other respects. Seidman 2011 included cross-over to docetaxel-capecitabine, but ORR and first-line PFS data stratified by hormone receptor status were included in the analysis. The results of Seidman 2011 and Chan 2009 were combined into a pooled analysis, which has been included, as it includes further outcomes stratified by hormone receptor status not reported in either of the original studies. CHAT included HER2-positive breast cancer only. BOLERO6 included ER-positive patients only. Fan 2013 and METRIC included TNBC patients only. All other trials contained both hormone receptor-positive and -negative patients.

Of the adjuvant trials, USON 01062, FINXX, CREATE-X, TACT2, and GEICAM 2003-10 have been published in peer-reviewed journals. The remaining adjuvant studies have been presented as conference abstracts or presentations only. The overall number of patients ranged from 636 in CBCSG-10 to 4391 in TACT2. Median follow-up varied from 2.5 years in the TNBC-only CBCSG-10 trial to 10.3 years in FINXX. USON 01062, FINXX, TACT2, and CBCSG-10 are adjuvant RCTs investigating the addition or substitution of capecitabine in the taxane component of standard anthracycline-taxane-containing regimens, and in the case of CBCSG-10, this was limited to a TNBC-only population. GEICAM 2003-10 investigated anthracycline-taxane (epirubicin-docetaxel) with sequential capecitabine versus epirubicin-cyclophosphamide and sequential docetaxel. CREATE-X and CIBOMA 2004-01 were adjuvant trials investigating capecitabine in patients following prior neoadjuvant chemotherapy, with CREATE-X including only those HER2-negative patients who did not achieve pCR with standard anthracycline-taxane-containing neoadjuvant chemotherapy, and CIBOMA 2004-01 including TNBC patients regardless of response to neoadjuvant chemotherapy. ICE was the only trial examining the addition of capecitabine to a bisphosphonate versus a bisphosphonate alone. USON 01062, FINXX, GEICAM 2003-10, TACT2, and ICE comprised predominantly Caucasian populations, whereas CBCSG-10 and CREATE-X were recruited from Asian countries only. CIBOMA 2004-01 was predominantly recruited from South America or Spain. ICE investigated "elderly" patients (aged 65 or over), whereas all other trials did not apply this restriction. Trastuzumab was provided for HER2-positive breast cancer patients in USON 01062, FINXX, TACT2, and GEICAM 2003-10. In ICE, 18.8% of patients were HER2-positive but did not receive HER2-targeted therapy. CREATE-X, CIBOMA 2004-01, and CBCSG-10 excluded HER2-positive patients.

All data acquired from neoadjuvant RCTs have been published in peer-reviewed journals. The overall number of patients ranged from 75 in Yoo 2015 to 1421 in GeparQuattro. Median follow-up varied from 4.4 years in Lee 2008 to 5.4 years in GeparQuattro. The primary endpoint of NSABP-40 was addition of capecitabine or gemcitabine to an anthracycline-taxane-containing neoadjuvant chemotherapy regimen with or without bevacizumab. All other trials did not include bevacizumab-containing regimens. Pathological complete response was the primary endpoint for all trials. Lee 2008, Zhang 2016, and Yoo 2015 were derived from Chinese Asian populations. All other trials involved primarily Caucasian populations.

All trials were open-label studies, and no trial randomised participants to an oral placebo in non-capecitabine arms. All adjuvant trials were phase 3 studies. BOLERO6, CHAT, Fan 2013, and Pallis 2012 were phase 2 metastatic studies, and Yoo 2015 was a phase 2 neoadjuvant trial.

With regards to sponsorship, Hoffman La Roche/Genentech were sole funders of SO140999, CHAT, TURANDOT, IMELDA, TABEA, and USON 01062, and they co-funded FINXX, GEICAM 2003-10, Lee 2008, ABCSG-24, GeparQuattro, and NSABP-40. Eisai Pharmaceuticals was the sole sponsor for Study 301 and EMBRACE. Eli Lily was the sole sponsor for Chan 2009 and Seidman 2011, and this company co-funded NSABP-40. Sanofi-Aventis co-funded FINXX, GEICAM 2003-10, Lee 2008, ABCSG-24, and GeparQuattro. AstraZeneca co-funded FINXX and ICE. Pfizer co-funded GEICAM 2003-10. Studies with no reported pharmaceutical funding included Fan 2013, Pallis 2012, CREATE-X, CBCSG-10, and Yoo 2015.

Excluded studies

See Characteristics of excluded studies.

We assessed the full text of 525 studies and immediately excluded 414 studies; the most common primary reasons for exclusion were irrelevant (105), duplicate (85), review paper or meta-analysis (80), wrong comparator (62), and RCT status unknown or still recruiting with no published results (55). After detailed assessment, we excluded a further 91 studies initially thought to be eligible based on initial protocol criteria; the most common primary reasons for exclusion were inadequate outcome data reported by hormone receptor status (50), wrong study design (24), and absence of reported results (23). A full breakdown of the reasons for exclusion is given in Figure 1.

Risk of bias in included studies

Figure 2, Figure 3 and Figure 4 summarise the risk of bias of all included studies.

Figure 2. Risk of bias graph for metastatic studies.

Figure 2. (Continued)

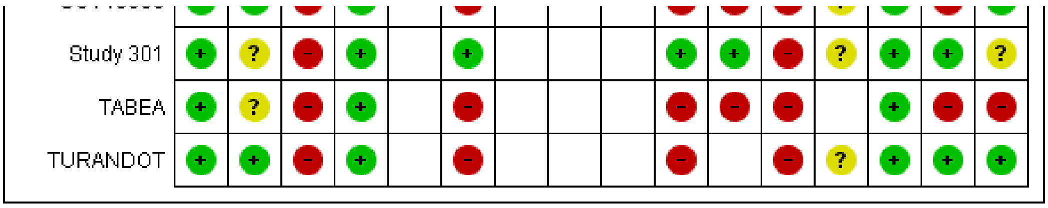
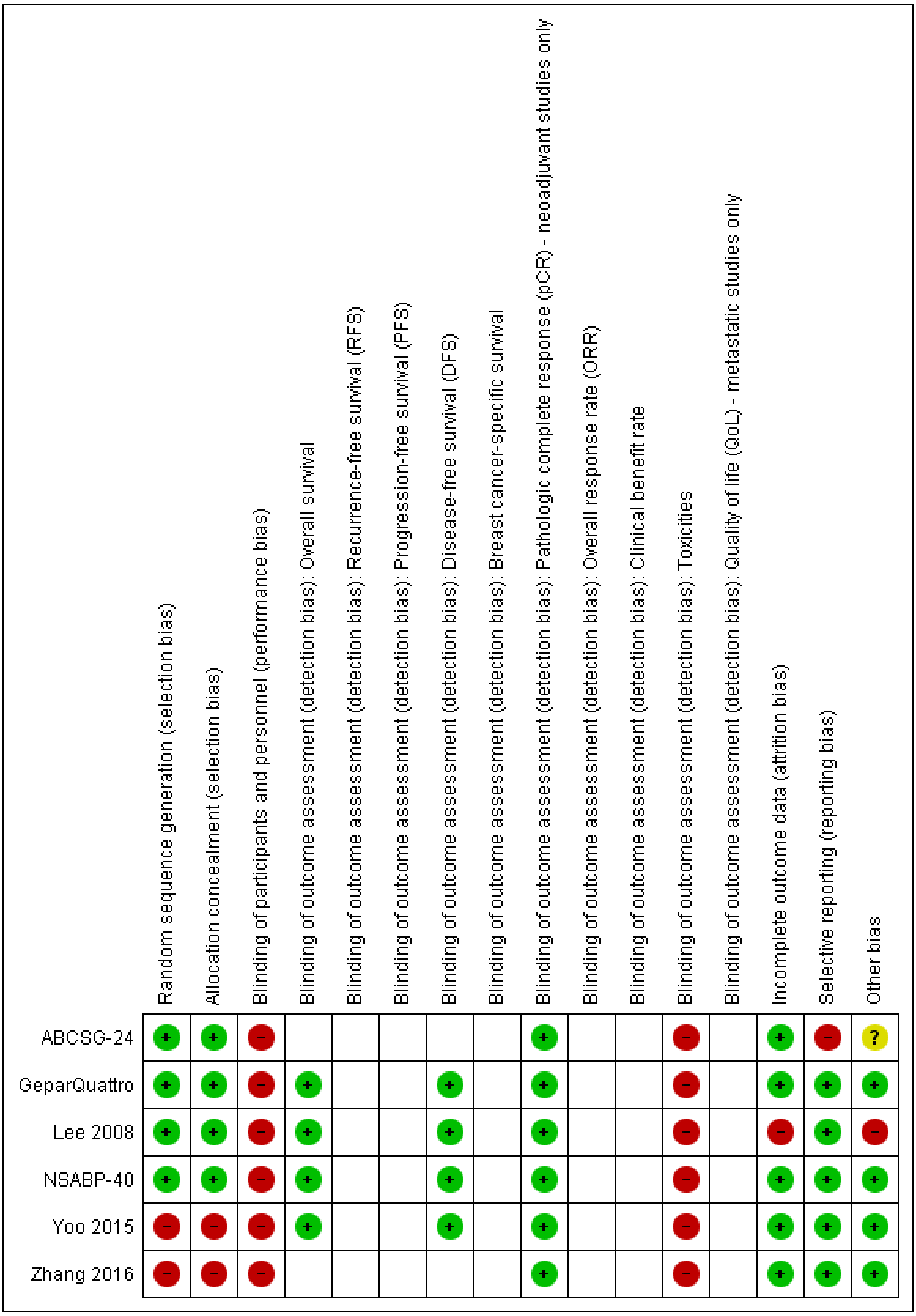


Figure 3. Risk of bias graph for adjuvant studies.

Figure 4. Risk of bias graph for neoadjuvant studies.



Allocation

Most of the included studies did not explicitly comment on allocation concealment. We judged those that had centralised randomisation to be at low risk of selection bias.

Metastatic settings

Three trials described centralised randomisation without explicit comment on allocation concealment (IMELDA; SO140999; TURANDOT). We judged these to be at low risk of selection bias.

Multiple trials did not provide any description of randomisation methods, but given that they were large multi-centre trials, we judged them to likely have used at least reasonable randomisation methods (Chan 2009; CHAT; Pallis 2012; Seidman 2011; Study 301; TABEA). As no description of randomisation method or allocation concealment was provided, we judged these studies to be at unclear risk of selection bias.

METRIC did not explicitly comment on randomisation method nor on allocation concealment. Given that this study was reported only by poster and abstract, we deemed it to be at unclear risk of selection bias.

We judged Fan 2013 to be at high risk of selection bias, as it was a single-centre trial with no explicit comment on randomisation process or allocation concealment.

Neoadjuvant settings

We judged Yoo 2015 and Zhang 2016 to be at high risk of selection bias, as both were single-centre trials that provided no explicit comment on the randomisation process nor on allocation concealment.

We judged all other trials in this setting to be at low risk of selection bias (ABCSG-24; GeparQuattro; Lee 2008; NSABP-40).

Adjuvant settings

We judged ICE to be at unclear risk, as it has yet to be fully reported, and no details regarding randomisation or allocation concealment were included in any of the information released thus far. CIBOMA 2004-01 also has yet to be fully reported, but this is a very large multi-centre multi-national trial, and we deemed it likely to include adequate randomisation methods but to be at unclear risk in terms of allocation concealment.

We judged all other trials in this setting to be at low risk of selection bias (CBCSG-10; CREATE-X; FINXX; GEICAM 2003-10; TACT2; USON 01062).

Blinding

We judged that all open-label studies were at high risk of performance bias. Regarding detection bias, we separated risks by outcomes relevant to each setting. We judged that given both the open-label nature of all studies and the large difference in toxicity profiles between capecitabine and heterogenous comparators, all toxicity outcomes would be at high risk, regardless of the setting.

Metastatic settings

We judged that the outcomes of PFS, OS, ORR, CBR, QoL, and toxicity were most relevant in this setting.

We considered that assessment of OS would not be affected by blinding and thus carried low risk. We considered that given the heterogeneity of treatment arms, all studies were unblinded, the outcome was highly subjective, and QoL was judged to be at unclear risk.

We considered that when tumour assessment was required (PFS, CBR, ORR), utilisation of centralised radiological assessment would render a trial at low risk; only two studies used centralised radiological assessment and thus were deemed at low risk (Pallis 2012; Seidman 2011). If it was not specified whether centralised radiological assessment was performed, we determined the study to be at high risk (Chan 2009; CHAT; Fan 2013; IMELDA; SO140999; Study 301; TABEA; TURANDOT).

Neoadjuvant settings

We judged that outcomes of pCR, DFS, and toxicity were most relevant in this setting. We considered that assessment of DFS would not be affected by blinding, and this would suggest low risk. All studies except ABCSG-24 and Zhang 2016 reported DFS. We judged that the outcome of pCR would not be affected by blinding, and thus all neoadjuvant studies would be at low risk (ABCSG-24; GeparQuattro; Lee 2008; NSABP-40; Yoo 2015; Zhang 2016).

Adjuvant settings

We judged that the outcomes of DFS, OS, and toxicity were most relevant in this setting. All studies reported these outcomes (CBCSG-10; CIBOMA 2004-01; CREATE-X; GEICAM 2003-10; ICE; TACT2; USON 01062), except FINXX, which reported RFS instead of DFS. CBCSG-10 reported both DFS and RFS. We considered that the outcomes of DFS, RFS, and OS would not be affected by blinding and thus carried low risk of detection bias.

Incomplete outcome data

We judged that all studies that reported outcomes by intention-to-treat population with accountability for attrition were at low risk of attrition bias.

Metastatic settings

We judged CHAT and Pallis 2012 to be at high risk, as not all patients were included in the intention-to-treat analysis. We judged the remaining studies to be at low risk of attrition bias.

We judged METRIC to be at unclear risk, as this study has not been published at the time of writing, and study authors did not report attrition numbers.

Neoadjuvant settings

We judged Lee 2008 to be at high risk, as not all randomised patients were included in the intention-to-treat analysis.

Adjuvant settings

We judged CBCSG-10 and CIBOMA 2004-01 to be at unclear risk, as these studies had not been published at the time of writing and consequently attrition numbers were not reported. ICE has not been published at the time of writing, but we believe that reporting of those who ceased treatment was adequate. We judged all other studies to be at low risk of attrition bias (CREATE-X; FINXX; GEICAM 2003-10; ICE; TACT2; USON 01062).

Selective reporting

We judged that all studies that adequately reported primary and secondary outcomes as well as toxicities were at low risk of reporting bias.

Metastatic settings

We deemed SO140999 to be at high risk of reporting bias because reporting by hormone receptor status was incomplete. We deemed IMELDA to be at high risk of reporting bias, as the secondary endpoints of quality of life and overall survival were not fully reported. We judged Seidman 2011 to be at high risk, as not all patients were assessed for response, and of those who were assessed, not all were assessed for the primary endpoint of time to progression. We judged TABEA to be at high risk of reporting bias, as the secondary endpoint of clinical benefit rate was not reported.

We judged CHAT to be at unclear risk of reporting bias, as some data were not yet mature at the time of writing. METRIC was not yet published, but these authors appeared to have reported all relevant primary and secondary outcomes, and we judged this study to be at low risk of reporting bias.

We judged Chan 2009 to be at unclear risk of reporting bias, as outcomes by hormone receptor status were not pre-planned.

We judged the remaining six trials to be at low risk of reporting bias.

Neoadjuvant settings

We deemed ABCSG-24 to be at high risk due to inadequate toxicity reporting, as well as to reporting of multiple additional non-pre-specified endpoints and use of a non-pre-specified definition for "pCR breast and nodes". Additionally, we excluded HER2-positive patients from the "non-TNBC" group; thus reporting is incomplete.

We judged the other studies to be at low risk of reporting bias.

Adjuvant settings

We judged CBCSG-10 to have unclear risk, as this study had not been published at the time of writing, and all primary and secondary endpoints were not yet reported. We judged all other studies to have low risk of reporting bias.

Other potential sources of bias

Metastatic settings

Chan 2009 and Seidman 2011 underwent subsequent pooled analysis. We judged these studies to be at unclear risk of other bias due to the post-hoc unplanned nature of the additional analyses. Additionally, we judged Seidman 2011 to be at unclear risk, as we judged that cross-over could potentially dilute survival outcomes.

Study 301 underwent subsequent extensive unplanned post-hoc analyses. Thus, we judged this study to be at unclear risk of bias.

We judged METRIC to be at unclear risk, as it had not been published at the time of writing.

We judged TABEA to be at high risk due to early termination of the study due to futility. Additionally, patients initially treated with docetaxel then received paclitaxel due to changes in the licensing of taxane-bevacizumab, creating heterogeneity in the control arm.

We detected no other potential sources of bias in the remaining trials.

Neoadjuvant settings

We deemed Lee 2008 to be at high risk of other bias due to unclear reporting of adjuvant treatments, including other chemotherapy, endocrine treatment, and trastuzumab. These weaknesses could influence DFS and OS but did not affect pCR, the primary endpoint of the study. We deemed ABCSG-24 to be at unclear risk of other bias, as clinically relevant endpoints (OS, DFS) were not included. Zhang 2016 also did not report these outcomes but did specify that reporting was planned in due course when the adjuvant component of the trial was complete. As such, we judged this not to be a potential source of bias.

We detected no other potential sources of bias in the remaining three trials.

Adjuvant settings

We judged CBCSG-10, CIBOMA 2004-01, and ICE to be at unclear risk, as they were unpublished at the time of writing.

We judged that CREATE-X had a number of issues that could bias outcomes in certain cohorts, and thus DFS outcomes. First, the study excluded from neoadjuvant chemotherapy patients who achieved pCR, thus selecting patients with a potentially worse prognosis. Additionally, in the TNBC cohort design, capecitabine was compared with no treatment, whereas in the hormone receptor-positive cohort design, capecitabine + AI/tamoxifen was compared with AI/tamoxifen. The consensus was that this could cause potential bias towards the study arm in the TNBC cohort and could influence DFS outcomes.

We detected no other potential sources of bias in the remaining trials.

Effects of interventions

See: **Summary of findings 1** Capecitabine-containing regimens compared to chemotherapy regimens without capecitabine for metastatic breast cancer; **Summary of findings 2** Capecitabine-containing regimens compared to non-capecitabine-containing regimens for neoadjuvant treatment; **Summary of findings 3** Capecitabine-containing regimens compared to non-capecitabine-containing regimens or no chemotherapy for early breast cancer

Metastatic setting

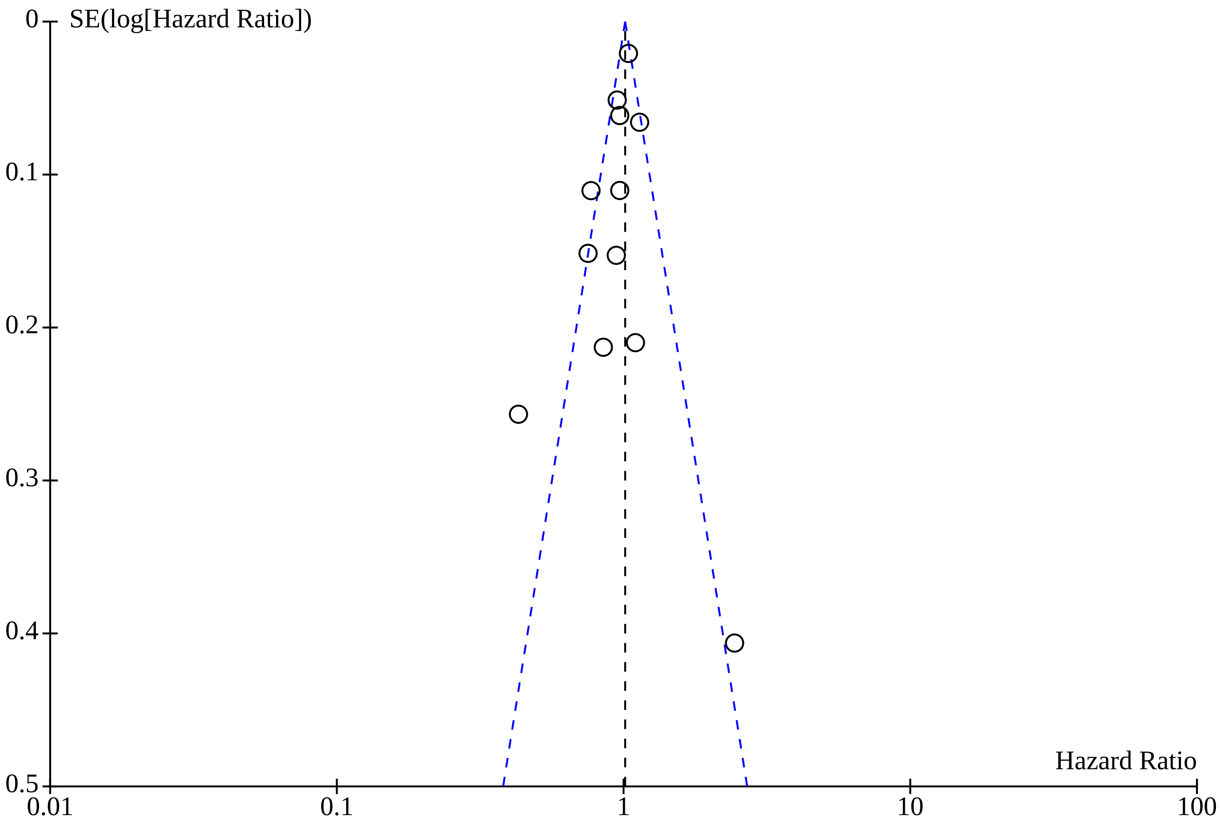
Twelve studies (75 records) referred to 10 different treatment comparisons in the metastatic setting (BOLERO6; Chan 2009; CHAT; Fan 2013; IMELDA; METRIC; Pallis 2012; Seidman 2011; SO140999; Study 301; TABEA; TURANDOT). See Summary of findings 1.

Of the 12 studies, four used capecitabine monotherapy, four added capecitabine to a chemotherapy regimen, and the remaining four substituted capecitabine into a chemotherapy regimen.

Overall survival

Twelve studies with 4325 participants reported data on overall survival (OS). These demonstrated no difference in mortality in capecitabine-containing regimens compared to non-capecitabine-containing regimens (hazard ratio (HR) 1.01, 95% confidence interval (CI) 0.98 to 1.05; high-certainty evidence; Analysis 1.1), although with relatively high heterogeneity (I^2 = 67%). The four studies adding capecitabine to standard chemotherapy regimens demonstrated moderate improvement in mortality (HR 0.78, 95% CI 0.66 to 0.92; Analysis 3.1). Neither capecitabine monotherapy nor capecitabine substitution demonstrated this benefit (four studies - capecitabine monotherapy; HR 1.00, 95% CI 0.93 to 1.08; Analysis 2.1; four studies - capecitabine substitution; HR 1.03, 95% CI 0.99 to 1.07; Analysis 4.1). Heterogeneity remained high across all subgroup analyses of capecitabine addition by trial design type when unsegregated by hormone receptor status. A funnel plot and Egger's test did not support any publication bias for the studies reviewed (Figure 5; Egger's test: P = 0.47).

Figure 5. Funnel plot of comparison: 6 Metastatic all: capecitabine-containing regimen vs non-capecitabine-containing regimen, outcome: 6.1 OS all.



Hormone receptor-positive disease

Seven studies with 1834 participants reported data on OS in patients with hormone receptor-positive disease. These studies demonstrated no difference in mortality for capecitabine-containing regimens compared to non-capecitabine-containing regimens (HR 0.93, 95% CI 0.84 to 1.04; high-certainty evidence; Analysis 1.2), although with high heterogeneity (I^2 = 65%). The addition of capecitabine demonstrated a substantial difference in OS in patients with hormone receptor-positive disease (HR 0.62, 95% CI 0.47 to 0.81; Analysis 3.2), with low heterogeneity. However, only two studies reported outcomes in this particular setting. Neither capecitabine as monotherapy nor substitution of capecitabine into standard chemotherapy regimens demonstrated any benefit in OS for hormone receptor-positive disease (three studies - capecitabine monotherapy; HR 1.00, 95% CI 0.86 to 1.17; Analysis 2.2; two studies - capecitabine substitution; HR 1.02, 95% CI 0.84 to 1.23; Analysis 4.2), although with high heterogeneity in both cases (I^2 > 50%).

Hormone receptor-negative disease

Eight studies with 1577 participants reported data on OS in patients with hormone receptor-negative disease. These studies demonstrated no difference in mortality in the overall comparison between capecitabine-containing regimens and non-capecitabine-containing regimens (HR 1.00, 95% CI 0.88 to 1.13; high-certainty evidence; Analysis 1.3), with high heterogeneity (I^2 = 63%). The addition of capecitabine showed a non-significant trend towards benefit (two studies - HR 0.79, 95% CI 0.59 to 1.06; Analysis 3.3), with high heterogeneity (I^2 = 70%), whereas neither capecitabine monotherapy (three studies - HR 1.09, 95% CI 0.91 to 1.29; Analysis 2.3) nor substitution with capecitabine (three studies - HR 1.00, 95% CI 0.79 to 1.26; Analysis 4.3) showed any difference in OS, although again both with high heterogeneity (I^2 > 50%).

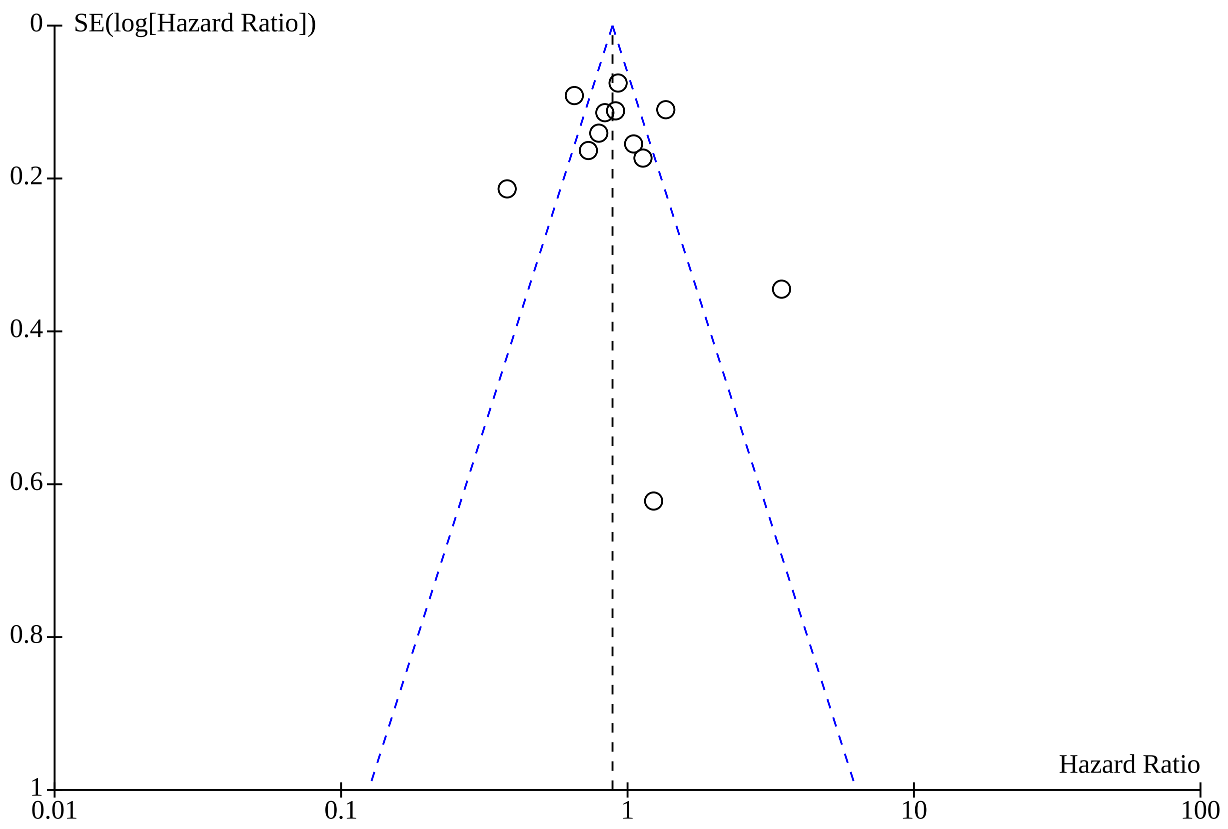
Triple-negative disease

Five studies reported OS outcomes with patients with triple-negative disease, and these studies demonstrated increased mortality with capecitabine (HR 1.20, 95% CI 1.01 to 1.43; Analysis 1.6), again with high heterogeneity (I^2 = 69%). There was no difference in OS for capecitabine monotherapy (two studies - HR 1.19, 95% CI 0.98 to 1.45; Analysis 2.4), with high heterogeneity (I^2 = 76%), or substitution with capecitabine (two studies - HR 1.59, 95% CI 1.03 to 2.43; Analysis 4.4), with low heterogeneity. Only IMELDA reported OS for the addition of capecitabine in triple-negative disease, which showed a strong trend towards OS benefit (HR 0.44, 95% CI 0.19 to 1.02).

Progression-free survival

Twelve studies with 4325 participants reported data on progression-free survival (PFS). These demonstrated a small improvement in PFS in capecitabine-containing regimens compared to non-capecitabine-containing regimens (HR 0.89, 95% CI 0.82 to 0.96; moderate-certainty evidence; Analysis 1.7), with high heterogeneity (I^2 = 84%). A funnel plot and Egger's test did not support any publication bias for the studies reviewed (Figure 6; Egger's test: P = 0.26).

Figure 6. Funnel plot of comparison: 6 Metastatic all: capecitabine-containing regimen vs non-capecitabine-containing regimen, outcome: 6.7 PFS all.



A more substantial effect was seen with the addition of capecitabine (four studies - HR 0.69, 95% CI 0.60 to 0.78; Analysis 3.5), again with high heterogeneity (I^2 = 82%). However there was no difference in PFS with capecitabine monotherapy (four studies - HR 0.92, 95% CI 0.82 to 1.04; Analysis 2.5), with low heterogeneity, or with capecitabine substitution (four studies - HR 1.06, 95% CI 0.93 to 1.20; Analysis 4.5), with high heterogeneity (I^2 = 87%).

Hormone receptor-positive disease

Seven studies with 1594 participants reported data on PFS for patients with hormone receptor-positive disease. These data show a small improvement in PFS in the comparison between capecitabine-containing regimens and non-capecitabine-containing regimens (HR 0.82, 95% CI 0.73 to 0.91; moderate-certainty evidence; Analysis 1.8), with high heterogeneity (I^2 = 81%). This effect was present and was of similar magnitude for the use of capecitabine monotherapy (three studies - HR 0.84, 95% CI 0.72 to 0.99; Analysis 2.6), with low heterogeneity, and was more substantial for the addition of capecitabine (three studies - HR 0.67, 95% CI 0.55 to 0.82; Analysis 3.6), although with high heterogeneity (I^2 = 91%). The only study that substituted capecitabine into a chemotherapy regimen and reported outcome data for PFS in hormone receptor-positive disease was the pooled analysis (Seidman 2011), which did not demonstrate any improvement (HR 0.95, 95% CI 0.78 to 1.17; Analysis 4.6).

Hormone receptor-negative disease

Seven studies with 1122 participants reported data on PFS in patients with hormone receptor-negative disease. These studies showed no difference in PFS in the comparison between capecitabine-containing regimens and non-capecitabine-containing regimens (HR 0.96, 95% CI 0.83 to 1.10; moderate-certainty evidence; Analysis 1.9), with low heterogeneity. This finding was consistent across both capecitabine monotherapy (three studies - HR 1.01, 95% CI 0.84 to 1.21; Analysis 2.7), with low heterogeneity, and substitution of capecitabine into a chemotherapy regimen (two studies - HR 1.02, 95% CI 0.79 to 1.31; Analysis 4.7), with high heterogeneity (I^2 = 93%). The addition of capecitabine demonstrated improvement in PFS in the two studies reporting this outcome for hormone receptor-negative patients (HR 0.60, 95% CI 0.39 to 0.93; Analysis 3.7), with low heterogeneity.

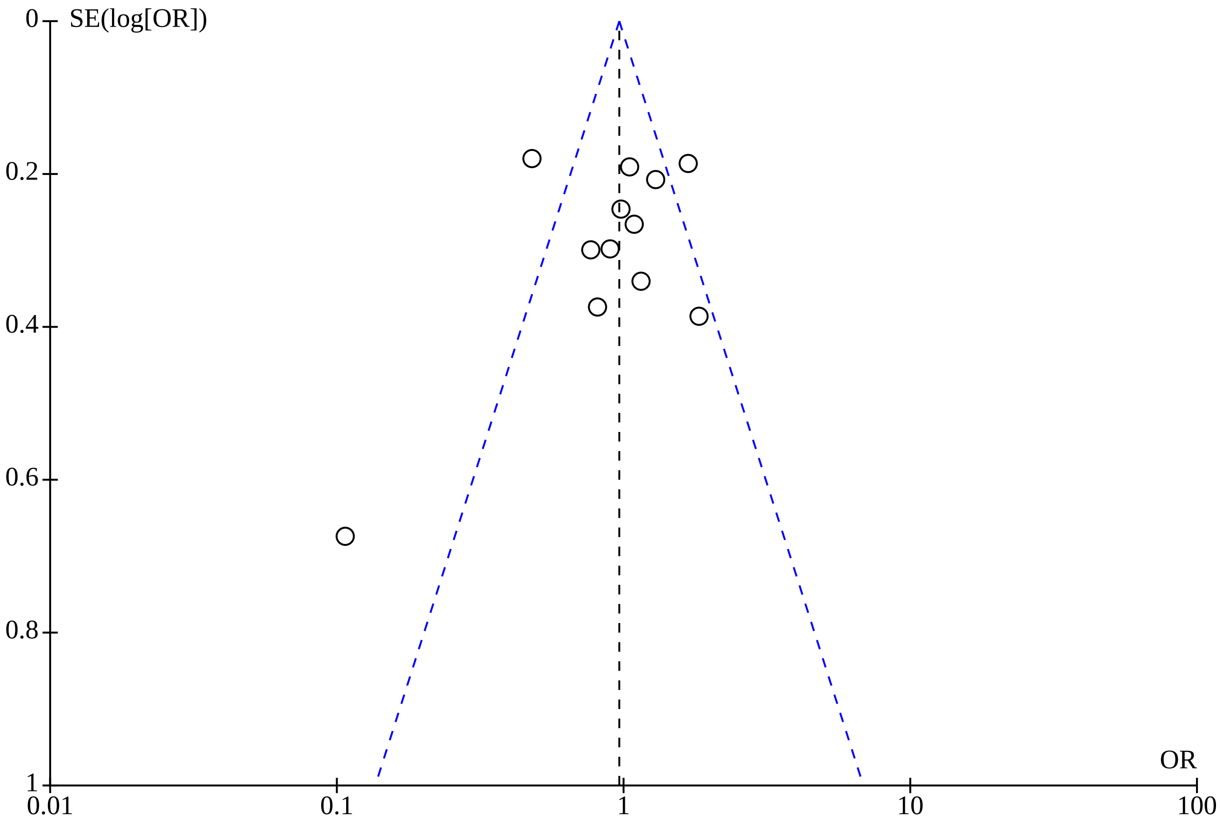
Triple-negative disease

Five studies reported data on PFS in patients with TNBC. These data show worse PFS for capecitabine-containing regimens relative to non-capecitabine-containing regimens overall (HR 1.22, 95% CI 1.04 to 1.44; Analysis 1.12), with high heterogeneity (I^2 = 78%). This result was driven by the two studies of capecitabine substitution (HR 1.78, 95% CI 1.28 to 2.47; Analysis 4.8), although high heterogeneity remained (I^2 = 84%). There was no difference in PFS in TNBC for capecitabine monotherapy (two studies - HR 1.16, 95% CI 0.94 to 1.41; Analysis 2.8), with low heterogeneity. Only one study in the addition of capecitabine subgroup reported PFS for TNBC (IMELDA). This study showed no difference but trended towards benefit in contrast to the other subgroups (HR 0.57, 95% CI 0.31 to 1.05).

Objective response rate

Twelve studies with 4200 participants reported data on objective response rate (ORR). These studies demonstrated no overall difference in ORR for the comparison between capecitabine-containing regimens and non-capecitabine-containing regimens (odds ratio (OR) 0.97, 95% CI 0.84 to 1.11; moderate-certainty evidence; Analysis 1.13), with high heterogeneity (I^2 = 73%). A funnel plot and Egger's test did not support any publication bias for the studies reviewed (Figure 7; Egger's test: P = 0.73).

Figure 7. Funnel plot of comparison: 6 Metastatic all: capecitabine-containing regimen vs non-capecitabine-containing regimen, outcome: 6.13 ORR all.



The use of capecitabine monotherapy compared to non-capecitabine regimens demonstrated no difference in ORR (four studies - OR 0.96, 95% CI 0.74 to 1.26; Analysis 2.9), with low heterogeneity. In contrast, the addition of capecitabine demonstrated a modest improvement in ORR (four studies - OR 1.37, 95% CI 1.07 to 1.75; Analysis 3.9), also with low heterogeneity, whereas in the four studies of capecitabine substitution, ORR was decreased (OR 0.73, 95% CI 0.58 to 0.91; Analysis 4.9), with high heterogeneity (I^2 = 87%).

No specific ORR data were available for hormone receptor-positive or -negative disease. Participants with TNBC had lower ORR with capecitabine-containing regimens compared to non-capecitabine-containing regimens (three studies - OR 0.42, 95% CI 0.27 to 0.65; Analysis 1.14), with high heterogeneity (I^2 = 80%).

Complete response rate

Six studies documented 77 of 2242 participants achieving a complete response (CR), with no difference in benefit with capecitabine-containing relative to non-capecitabine-containing therapy (OR 1.36, 95% CI 0.85 to 2.18; Analysis 1.16), with low heterogeneity. Benefit was seen in the hormone receptor-positive group (two studies - OR 4.75, 95% CI 1.17 to 19.33; Analysis 1.17), but not in the hormone receptor-negative group (two studies - OR 0.82, 95% CI 0.39 to 1.73; Analysis 1.18), with low heterogeneity in both cases.

Clinical benefit rate

Four studies reported clinical benefit rate (CBR) but demonstrated no difference between capecitabine- and non-capecitabine-containing regimens (OR 0.96, 95% CI 0.76 to 1.21; Analysis 1.15), with low heterogeneity.

Quality of life

Five studies reported quality of life data (see Table 2). Four studies used the European Organisation for Research and Treatment of Cancer core quality of life questionnaire (EORTC QLQ-C30), and the other study used the Rotterdam Symptom Checklist. Given differences in measurement and in the degree to which this outcome was reported, a quantitative estimate of effect was not calculated for this review. However, in general, no differences in global health scores were evident between the two treatment groups at around two years of follow-up (low-certainty evidence).

Toxicity

All 12 studies reported some toxicity data (see Table 3). Given the variability in reporting and the heterogeneous nature of the comparators, no new toxicity concerns were noted. Capecitabine-containing intervention arms showed an overall trend towards higher rates of diarrhoea and hand-foot syndrome, which would be expected from the known toxicity profile.

Neoadjuvant setting

Six included studies (31 records) referred to six treatment comparisons in the neoadjuvant setting (ABCSG-24; GeparQuattro; Lee 2008; NSABP-40; Yoo 2015; Zhang 2016). See Summary of findings 2.

Pathological complete response

All six studies provided some data related to pathological response. Some studies defined and reported pathological complete response (pCR) for breast, nodes, and breast plus nodes separately. We considered pathological complete response to be inclusive of both breast and breast plus nodes.

Across six studies with 3152 participants, capecitabine-containing regimens resulted in little difference in pCR in comparison to non-capecitabine-containing regimens (OR 1.12, 95% CI 0.94 to 1.33; high-certainty evidence; Analysis 9.1), although with high heterogeneity ($I^2 = 64\%$). Yoo 2015 was deemed at high risk of bias, but this was a relatively small study and was not thought to affect the overall result.

Hormone receptor-positive disease

Four studies with 964 participants showed that capecitabine-containing regimens resulted in little to no difference in pCR for cancers that were hormone receptor-positive in comparison to non-capecitabine-containing regimens (OR 1.22, 95% CI 0.76 to 1.95; moderate-certainty evidence; Analysis 9.2), with high heterogeneity ($I^2 = 57\%$). Two studies did not report pCR by hormone receptor status - these represented more than half of the neoadjuvant cohort, and thus the results need to be considered in light of this (ABCSG-24; GeparQuattro).

Hormone receptor-negative disease

Four studies with 646 participants demonstrated that capecitabine-containing regimens resulted in little to no difference in pCR for cancers that were hormone receptor-negative in comparison to non-capecitabine-containing regimens (OR 1.28, 95% CI 0.61 to 2.66; moderate-certainty evidence; Analysis 9.3), with low heterogeneity. Three out of four studies trended towards benefit with capecitabine, albeit all with low numbers. Two studies did not report pCR by hormone receptor status (ABCSG-24; GeparQuattro); these represent more than half of the neoadjuvant cohort, and thus the results need to be considered in light of this.

Four studies with 1063 participants demonstrated that capecitabine-containing regimens resulted in little to no difference in pCR for cancers that were triple-negative in comparison to non-capecitabine-containing regiments (OR 1.03, 95% CI 0.72-1.46; Analysis 9.4), albeit with high heterogeneity ($I^2 = 73\%$).

Disease-free survival

Four studies reported data on disease-free survival (DFS) (GeparQuattro; Lee 2008; NSABP-40; Yoo 2015). Based on these four studies with 2460 participants, capecitabine-containing regimens showed no difference in DFS compared to non-capecitabine-containing regimens (HR 1.02, 95% CI 0.86 to 1.21; high-certainty evidence; Analysis 9.5), with low heterogeneity. Zhang 2016 did not report data for this outcome, as the data were not yet mature, and ABCSG-24 did not comment on plans to collect or report these data. Note that the median follow-up is only 3 to 5.4 years, with the lower limit early for relapse expected for this cohort.

Outcome data were insufficient for analysis of DFS by hormone receptor subtype.

Overall survival

Four studies with 2460 participants reported data on overall survival (OS) (GeparQuattro; Lee 2008; NSABP-40; Yoo 2015). These data demonstrate that capecitabine-containing regimens resulted in no difference in OS compared to non-capecitabine-containing regimens (HR 0.97, 95% CI 0.77 to 1.23; high-certainty evidence; Analysis 9.6), again with low heterogeneity. Similar to DFS, Zhang 2016 did not report data for this outcome, as the data were not yet mature, and ABCSG-24 did not comment on plans to collect or report these data. Note that the median follow-up is only 3 to 5.4 years, with the lower limit early for death for this cohort.

Again, outcome data were insufficient for analysis of OS by hormone receptor subtype.

Adverse events

Febrile neutropenia

Four studies with 2890 participants reported rates of grade 3 or 4 febrile neutropenia. These data demonstrated no significant difference in febrile neutropenia between capecitabine- and non-capecitabine-containing regimens (OR 1.31, 95% CI 0.97 to 1.77; moderate-certainty evidence; Analysis 9.9), with low heterogeneity. The other two studies did not specifically report febrile neutropenia, with ABCSG-24 grouping all haematological adverse effects and Zhang 2016 reporting only leukopenia.

Diarrhoea

Three studies with 2686 participants reported rates of grade 3 or 4 diarrhoea. These data demonstrated a definitive increase in diarrhoea with capecitabine- compared to non-capecitabine-containing regimens (OR 1.95, 95% CI 1.32 to 2.89; moderate-certainty evidence; Analysis 9.13), with low heterogeneity. The other three studies did not specifically report diarrhoea, with ABCSG-24 grouping together all gastrointestinal adverse effects; Zhang 2016 grouping nausea, vomiting, and diarrhoea together; Lee 2008 reported only "all-grade" diarrhoea and did not specify grade 3 or 4 diarrhoea.

Hand-foot syndrome

Five studies with 3021 participants reported rates of grade 3 or 4 hand-foot syndrome. These data demonstrated a definitive increase in hand-foot syndrome with capecitabine- compared to non-capecitabine-containing regimens (OR 6.77, 95% CI 4.89 to 9.38; moderate-certainty evidence; Analysis 9.11), although it is somewhat surprising that this involved high heterogeneity (I^2 = 80%). ABCSG-24 was the only study not to report this; this study did report a marked increase (n = 23 versus n = 0) in "Skin and subcutaneous tissue disorders" in the capecitabine arm, which presumably relates to hand-foot syndrome, but this was not specified in the paper.

Adjuvant setting

Eight studies (45 records) referred to six different treatment comparisons in the adjuvant setting (CBCSG-10; CIBOMA 2004-01; CREATE-X; FINXX; GEICAM 2003-10; ICE; TACT2; USON 01062). See:Summary of findings 3.

Of the eight studies, four studies gave capecitabine as monotherapy and four utilised capecitabine as a substitution into or an addition to a chemotherapy regimen.

Disease-free survival

Eight studies with 13,547 participants reported data on disease-free survival (DFS) or recurrence-free survival (RFS). These data demonstrated no overall difference in DFS between capecitabine-containing regimens and non-capecitabine-containing regimens across all patients (HR 0.93, 95% CI 0.86 to 1.01; moderate-certainty evidence; Analysis 6.1), with relatively high heterogeneity (I^2 = 54%). FINXX was the only study in this review that consistently reported RFS, and this was combined with DFS in a sensitivity analysis.

Of the eight studies, four utilised capecitabine as monotherapy in the adjuvant setting. The use of capecitabine monotherapy did not show a significant difference in DFS between capecitabine-containing regimens and non-capecitabine-containing regimens (HR 0.91, 95% CI 0.82 to 1.01; Analysis 8.1), with low heterogeneity. The remaining four studies utilised capecitabine as an addition to or a substitution into the existing chemotherapy regimen. Capecitabine in this setting also did not show a difference in DFS (HR 0.94, 95% CI 0.83 to 1.07; Analysis 7.1), although with high heterogeneity (I^2 = 69%).

Hormone receptor-positive disease

Five studies with 5604 participants demonstrated no difference in DFS among patients with hormone receptor-positive disease with capecitabine-containing regimens compared to non-capecitabine-containing regimens (HR 1.03, 95% CI 0.91 to 1.17; moderate-certainty evidence; Analysis 6.2), with low heterogeneity.

In the setting of capecitabine monotherapy, two studies reported results on DFS in hormone receptor-positive patients. These studies did not demonstrate any difference between capecitabine- and non-capecitabine-containing regimens (HR 0.96, 95% CI 0.78 to 1.18; Analysis 8.2), with low heterogeneity. Three studies in which capecitabine was used as an addition to or a substitution into the existing chemotherapy regimen reported outcomes among hormone receptor-positive patients. These studies also did not show any difference in DFS (HR 1.07, 95% CI 0.92 to 1.25; Analysis 7.2), although with high heterogeneity (I^2 = 55%).

Hormone receptor-negative disease

Seven studies with 2879 participants demonstrated improvement in DFS among patients with hormone receptor-negative disease with capecitabine-containing regimens compared to non-capecitabine-containing regimens (HR 0.74, 95% CI 0.64 to 0.86; moderate-certainty evidence; Analysis 6.3), with low heterogeneity.

All four studies that utilised capecitabine as monotherapy reported DFS outcomes for hormone receptor-negative patients. These studies demonstrated modest benefit with use of capecitabine as monotherapy (HR 0.84, 95% CI 0.72 to 0.98; Analysis 8.3), with high heterogeneity (I^2 = 51%). The four studies in which capecitabine was used as an addition to or a substitution into the existing chemotherapy regimen reported similar benefit for DFS (HR 0.74, 95% CI 0.59 to 0.93; Analysis 7.3), with low heterogeneity.

Triple-negative disease

In patients with TNBC, seven studies demonstrated significant improvement in DFS with capecitabine-containing regimens compared to non-capecitabine-containing regimens (HR 0.83, 95% CI 0.72 to 0.95; Analysis 6.4), with low heterogeneity. Two of these studies had an entirely triple-negative cohort (CBCSG-10; CIBOMA 2004-01). The benefit appeared of greater magnitude when capecitabine was used as an addition/substitution (4 studies; HR 0.76, 95% CI 0.61 to 0.94; Analysis 7.4), with low heterogeneity, than when it was employed as monotherapy (3 studies; HR 0.85, 95% CI 0.71 to 1.01; Analysis 8.4), with high heterogeneity (I^2 = 66%).

Overall survival

Eight studies with 13,547 participants reported data on OS. A modest reduction in mortality was observed for capecitabine-containing regimens relative to non-capecitabine-containing regimens across all patients (HR 0.89, 95% CI 0.81 to 0.98; moderate-certainty evidence; Analysis 5.1), albeit with high heterogeneity (I^2 = 52%). In the setting of capecitabine monotherapy, studies demonstrated no difference in mortality between capecitabine- and non-capecitabine-containing regimens (HR 0.93, 95% CI 0.83 to 1.05; Analysis 8.5), with borderline high heterogeneity (I^2 = 50%), whereas improved OS was seen with use of capecitabine as an addition to or a substitution into the existing regimen (4 studies; HR 0.83, 95% CI 0.71 to 0.96; Analysis 7.5), again with high heterogeneity (I^2 = 56%).

Hormone receptor-positive disease

Three studies reported data on OS for patients with hormone receptor-positive disease. These studies demonstrated no difference in mortality with capecitabine-containing regimens compared to non-capecitabine-containing regimens (HR 0.86, 95% CI 0.68 to 1.09; Analysis 5.2), with low heterogeneity. Only CREATE-X reported outcomes for hormone receptor-positive disease with capecitabine monotherapy, which did not demonstrate significant benefit, albeit with wide confidence intervals (HR 0.73, 95% CI 0.38 to 1.40). Two studies reported outcomes for hormone receptor-positive disease with capecitabine as an addition to or a substitution into the existing regimen, and also showed no difference in OS (HR 0.88, 95% CI 0.69 to 1.13; Analysis 7.6), with low heterogeneity.

Hormone receptor-negative disease

Five studies reported data on OS for patients with hormone receptor-negative disease. These studies demonstrated improvement in OS with capecitabine-containing regimens compared with non-capecitabine-containing regimens (HR 0.72, 95% CI 0.59 to 0.89; Analysis 5.3), again with low heterogeneity. Two of these employed capecitabine added as monotherapy (in entirely triple-negative populations), which produced no significant benefit (HR 0.79, 95% CI 0.59 to 1.05; Analysis 8.7), with high heterogeneity (I^2 = 67%), and three utilised capecitabine as an addition to or a substitution into the existing regimen, with significant benefit (HR 0.66, 95% CI 0.49 to 0.88; Analysis 7.7), with low heterogeneity.

Triple-negative disease

Five studies reported data on OS for patients with triple-negative disease, two of which recruited entirely triple-negative cohorts. These studies demonstrated a large improvement in OS with capecitabine-containing regimens compared with non-capecitabine-containing regimens (HR 0.70, 95% CI 0.57 to 0.86; Analysis 5.4), with low heterogeneity. Two of these studies added capecitabine as monotherapy, as above, which produced no significant benefit (HR 0.79, 95% CI 0.59 to 1.05; Analysis 8.8), with high heterogeneity (I^2 = 67%), and three gave capecitabine as an addition to or a substitution into the existing chemotherapy regimen, with substantial significant OS benefit (HR 0.61, 95% CI 0.46 to 0.82; Analysis 7.8), with low heterogeneity.

Adverse effects

Febrile neutropenia

Five studies with 8086 participants reported rates of grade 3 and 4 febrile neutropenia. Data showed lower rates of febrile neutropenia with capecitabine-containing regimens compared to non-capecitabine-containing regimens (OR 0.55, 95% CI 0.47 to 0.64; moderate-certainty evidence; Analysis 5.7), although with high heterogeneity (I^2 = 93%). The three studies involving capecitabine monotherapy versus observation or non-chemotherapy treatment (bisphosphonate) did not report this outcome, likely because febrile neutropenia was not an expected adverse effect.

Diarrhoea

Eight studies with 11,207 participants reported rates of grade 3 and 4 diarrhoea. These data demonstrated higher rates of diarrhoea with capecitabine-containing regimens compared to non-capecitabine-containing regimens (OR 2.46, 95% CI 2.01 to 3.01; moderate-certainty evidence; Analysis 5.11), again with high heterogeneity (I^2 = 85%).

Hand-foot syndrome

Eight studies with 11,207 participants reported rates of grade 3 and 4 hand-foot syndrome. These data demonstrated much higher rates of hand-foot syndrome with capecitabine-containing regimens compared to non-capecitabine-containing regimens (OR 13.60, 95% CI 10.65 to 17.37; moderate-certainty evidence; Analysis 5.9), with high heterogeneity (I^2 = 75%).

DISCUSSION

Summary of main results

This review demonstrates treatment scenario-specific and breast cancer subtype-specific benefits for inclusion of capecitabine in chemotherapy.

In the metastatic setting, capecitabine was somewhat more efficacious in hormone receptor-positive relative to hormone receptor-negative and triple-negative disease, confirming the core hypothesis. Both complete response rate and progression-free survival (PFS) were significantly superior with inclusion of capecitabine for hormone receptor-positive tumours, with hazard ratios (HRs) of 4.75 and 0.82, and a modest trend towards improved survival at 0.93 and significantly improved survival at 0.62 for the modest number of patients in the trials in which capecitabine was added to the control regimen. No advantage was seen for any of these parameters in hormone receptor-negative disease, although with high heterogeneity for PFS. Inferior objective response rate (ORR), PFS, and overall survival (OS) were observed with capecitabine-containing regimens in triple-negative metastatic disease, although with high heterogeneity for all parameters.

Exploration of the metastatic setting in greater detail revealed substantially greater heterogeneity of design in assembled metastatic trials with capecitabine added to an existing regimen, substituted for a component of an existing regimen, or used as monotherapy. Studies exploring the addition of capecitabine to existing treatment appear to be the biggest contributor to the superior efficacy of capecitabine for metastatic hormone receptor-positive cancer. Heterogeneity was high for PFS but not for OS. In a hormone receptor subtype-specific analysis of the SO140999 trial, the addition of capecitabine to docetaxel led to significant and clinically useful OS benefit for hormone receptor-positive tumours (HR 0.65) but not for hormone receptor-negative disease (HR 0.90). The smaller, and as yet unpublished, TABEA trial, which compared similar arms, although with the addition of bevacizumab for all patients, showed the opposite effect, with superior PFS among hormone receptor-negative patients and a trend towards inferior outcomes in hormone receptor-negative patients, although OS has not been reported. This trial accounts for the high heterogeneity in PFS relative to OS for capecitabine addition trials in hormone receptor-positive disease. With more even effects seen by subtype, the addition of capecitabine to bevacizumab as consolidation after docetaxel and bevacizumab in the relatively small IMELDA study resulted in significant benefits for both PFS and OS in hormone receptor-positive tumours and trends towards PFS benefits as well as significant OS benefits in hormone receptor-negative and triple-negative cancers. The differences between SO140999 and TABEA are difficult to reconcile with available data. As bevacizumab has greater impact in oestrogen receptor negative (ER-) disease for PFS (although no overall impact for OS), this may have generated the observed differences, although further trials to clarify this issue are unlikely to be conducted.

Single-agent trials essentially represent head-to-head measures of drug efficacy, with PFS endpoints measuring basic efficacy and OS both addressing this and reflecting the optimal order of agents. In hormone receptor-positive cancer, capecitabine generally appeared a reasonable choice, with non-significantly superior PFS relative to exemestane/everolimus (BOLERO6), vinorelbine/gemcitabine (Pallis 2012), and eribulin (Study 301). This was reflected in non-significantly longer OS in the former two trials. The slightly shorter OS relative to eribulin in Study 301 may reflect lack of cross-over to eribulin (0.4%) relative to frequent reverse cross-over from eribulin to capecitabine (49.6%). Heterogeneity was low for PFS, possibly reflecting that capecitabine has robust activity in this disease subtype in the metastatic setting relative to a number of other agents. Higher heterogeneity for OS could stem from the differing line of treatment under study in clinical trials. In hormone receptor-negative and triple-negative patients, capecitabine again appeared a reasonable choice, showing no significant efficacy differences compared to other tested agents, with non-significant superiority to vinorelbine/gemcitabine in hormone receptor-negative cancers and non-significant inferiority to eribulin in triple-negative disease. Again, there was low heterogeneity for PFS, suggesting that capecitabine may be broadly comparable to a number of other agents for this disease subtype, whereas high heterogeneity for OS may reflect the diverse treatment lines involved in different trials. As monotherapy chemotherapy is favoured in the metastatic setting, it is unfortunate that no other studies have investigated the major agents in clinical practice in comparison to capecitabine monotherapy, namely, paclitaxel, docetaxel, and anthracyclines, to better delineate full efficacy.

Substitution trials are somewhat akin to single-agent trials comparing capecitabine to other agents in a standard combination. All trials indicate that capecitabine was equivalent for both disease-free survival (DFS) and OS in hormone receptor-positive and -negative disease, but was inferior in triple-negative disease, with generally low heterogeneity. This differential appeared more a consequence of differing trials conducted in different subtypes than necessarily differential sensitivity. Cisplatin was superior to capecitabine in combination with docetaxel in a small trial in triple-negative disease (Fan 2013), which also gave rise to the higher heterogeneity in OS for hormone receptor-negative tumours, whereas gemcitabine was equivalent to capecitabine when combined with docetaxel in hormone receptor-positive and -negative cancers (Seidman 2011), and capecitabine was equivalent to paclitaxel as a partner to bevacizumab across all subtypes (TURANDOT). The benefit of cisplatin in triple-negative breast cancer (TNBC) might be related to *BRCA* mutation status, but this was not assessed in Fan 2013.

In the neoadjuvant setting, studies were often small and designs complex, and research frequently involved multiple study arms, such that useful composite conclusions could not be made. Across all trials, capecitabine incorporation did not significantly affect pathological complete response (pCR) in any breast cancer subtype. Sparse reporting of longer-term follow-up did not reveal any influence on survival, and data did not permit useful subtype-specific analysis. However, on examination of individual trials, capecitabine/docetaxel showed greater efficacy in terms of pCR than doxorubicin and cyclophosphamide for hormone receptor-positive but not hormone receptor-negative tumours, in keeping with the greater efficacy of this combination in the metastatic setting (Lee 2008). The substitution of capecitabine for fluorouracil numerically increased pCR rates across subtypes and significantly increased pCR in triple-negative cancers (Zhang 2016). No other combinations significantly influenced pCR. Collectively, no role for capecitabine was apparent in the neoadjuvant setting based on available study data.

In contrast, in the adjuvant setting, inclusion of capecitabine significantly improved outcomes for hormone receptor-negative and triple-negative tumours, with DFS hazard ratios of 0.75 and 0.85 and OS hazard ratios of 0.71 and 0.69, respectively. By comparison, no significant benefit was observed for hormone receptor-positive cancers. Heterogeneity was low for DFS and OS outcomes in all subtypes for the adjuvant setting. Trials assessing adjuvant capecitabine comprised two distinctive clinical situations: immediately after surgery (CBCSG-10; FINXX; GEICAM 2003-10; ICE TACT2; USON 01062), and sequentially following (neo)adjuvant chemotherapy (CIBOMA 2004-01; CREATE-X). Overall adjuvant capecitabine monotherapy given without prior neoadjuvant chemotherapy showed no proven survival benefit. However adjuvant trials employing capecitabine in combination with docetaxel with an anthracycline-taxane-containing regimen displayed demonstrable OS benefit for hormone receptor-negative breast cancer and for TNBC (CBCSG-10; FINXX; USON 01062), with low heterogeneity for both. Composite results show impressive 36% and 41% reductions in mortality in hormone receptor-negative and triple-negative populations, respectively. This effect was consistent even with exclusion of CBCSG-10 from OS analysis, which is awaiting peer review publication. It is reassuring that the OS HR from CBCSG-10 is similar to that in TNBC subgroup analyses from USON 01062 and FINXX.

Heterogenous outcomes were attained by the single-agent addition of capecitabine after completion of standard neoadjuvant or adjuvant chemotherapy. In CREATE-X, when capecitabine was given to participants failing to achieve a pCR after standard neoadjuvant chemotherapy, results were commensurate with those seen for concurrent inclusion in the immediate post-surgery adjuvant setting, with mortality reduced by 48% in the triple-negative cohort. In contrast, the similarly sized CIBOMA 2004-01 study observed a non-significant 8% reduction in mortality for triple-negative disease when capecitabine was added after standard adjuvant or neoadjuvant chemotherapy. However, the CIBOMA 2004-01 study population differed, as most patients (81.2%; n = 712) received adjuvant chemotherapy before randomisation to capecitabine or observation. Of note also, in a pre-planned analysis. CIBOMA 2004-01 did find significant DFS and OS benefits with addition of capecitabine for patients with non-basal tumours. Theoretical reasons for this disparity include selection of only poorer prognosis non-pCR patients in CREATE-X, a moderately lower dose of capecitabine used in CIBOMA 2004-01 (1000 mg/m² twice daily versus 1250 mg/m² twice daily), the potential for CREATE-X to have had larger numbers of non-basal tumours, and the differing study populations - South American for CIBOMA 2004-01, and Japanese and Korean for CREATE-X. Notably, the three concurrent capecitabine

adjuvant studies produced homogenous results despite disparate ethnic populations (Chinese, European, and North American, respectively), suggesting that the former three explanations may hold the answer (CBCSG-10; FINXX; USON 01062).
This review did not identify new findings regarding toxicity. Capecitabine administration significantly increased the risk of hand-foot syndrome, mucositis, and diarrhoea. Ischaemic cardiac events were numerically increased but not significantly so. Treatment-related deaths were non-significantly fewer.

Quality of life assessments were confined to metastatic studies. Five of twelve studies reported quality of life outcomes, with no significant differences in these endpoints identified between groups in any trial. Heterogeneity of reported data precluded combined analysis.

The differential activity identified for capecitabine between hormone receptor-positive and -negative cancers was complex, with hormone receptor-positive metastatic disease and hormone receptor-negative early disease showing greatest sensitivity. Explanations for this difference may lie in the environment of the target cell in the two treatment scenarios. For metastatic disease, as well as for neoadjuvant treatment of the breast primary, malignant cells are actively growing as part of a macroscopic tumour mass. There is an established blood supply, and consequently hypoxia and nutritional deprivation are infrequent. By contrast, in the adjuvant scenario, eradication of single tumour cells and micro-metastatic deposits is the goal. Evidence suggests that these cells are often harboured in the bone marrow, are quiescent and so are not proliferating, and do not have an established blood supply, such that hypoxia and poor nutrition are common.

Given first the metastatic situation, although hormone receptor-negative breast cancer is generally considered more chemo-responsive, this concept is largely based on the higher pCR rate seen after neoadjuvant anthracycline- and/or taxane-based chemotherapy. For example, one meta-analysis demonstrated pCR rates of 8.3% versus 31.1% for human epidermal growth factor receptor 2 (HER2)-negative hormone receptor-positive and -negative cancers, respectively (OR 5.0, 95% CI 4.20 to 5.92; Houssami 2012). However, a meta-analysis of docetaxel chemo-responsiveness in the metastatic setting showed no difference between hormone receptor-positive and -negative disease, with response rates of 46.8% and 44.7%, respectively (Andre 2010). As noted above, an individual pooled analysis in metastatic disease found response rates for capecitabine to be significantly higher in hormone receptor-positive than in hormone receptor-negative disease (Blum 2012). Consequently, given these results and the noted synergy between docetaxel and capecitabine, the finding that capecitabine added efficacy preferentially to docetaxel in hormone receptor-positive breast cancer is not unexpected. A look at possible cell biological drivers to the sensitivity difference reveals that hormone receptor-positive tumours may be specifically more capecitabine-prone, as continuous lower-dose fluorouracil (the active moiety in capecitabine therapy) causes cell death via G2-M-phase cell cycle arrest and mitotic catastrophe, rather than via apoptotic death (Yoshikawa 2001), to which hormone receptor-positive cells are less prone, potentially due to higher levels of the anti-apoptotic protein Bcl-2 (Merino 2016).

In the adjuvant situation, after initial dissemination, many breast cancer cells enter a dormant phase, in which they are frequently resistant to adjuvant chemotherapy (Braun 2000). Triple-negative cancers have lower levels of dormancy than hormone receptor-positive disease (Kim 2012), such that disseminated tumour cells and micro-metastases are more likely to be cycling and consequently sensitive to chemotherapy. This would explain why patients with hormone receptor-negative cancers may derive larger benefit from adjuvant chemotherapy in general, with capecitabine-docetaxel synergy driving improved outcomes in CBCSG-10, FINXX, and USON 01062.

Beyond sensitivity to chemotherapy due to proliferation rates and apoptotic sensitivity, there is a possible role for pharmacokinetics in the observed differences. Capecitabine is a pro-drug that is metabolised to fluorouracil by thymidine phosphorylase (TP), including in tumour cells. Fluorouracil then inhibits thymidine synthetase (TS), thereby reducing thymidine production for DNA synthesis. Following this, fluorouracil is deactivated by dihydropyrimidine dehydrogenase (DPD). Consequently, low TP or high TS or DPD could adversely affect prognosis. TS levels were higher in triple-negative than in hormone receptor-positive breast cancers (64% versus 16%; P = 0.023) and corresponded to shorter PFS (Lee 2011). This could contribute to lack of impact of capecitabine in the metastatic setting. Neither TP expression (as in Lee 2011) nor DPD activity or expression (as in Horiguchi 2004) was different between hormone receptor-positive and -negative cancers.

Overall completeness and applicability of evidence

A substantial number of otherwise suitable studies did not report outcomes by hormone receptor subtype despite having available data on individual patients, raising the possibility of publication bias and reducing the power of conclusions derived. However, with this proviso, sufficient trial data were available to allow comparisons by hormone receptor status as discussed with moderate to high levels of certainty in the three treatment scenarios.

Clinical trial design incorporating capecitabine in the adjuvant setting was heterogenous. Capecitabine was employed in combination with docetaxel in taxane-anthracycline regimens, as monotherapy, and in sequence following neoadjuvant or adjuvant regimens. However all three phase 3 trials that demonstrated OS benefit in TNBC employed capecitabine in combination with docetaxel (CBCSG-10; FINXX; USON 01062). Notably, trials that demonstrated capecitabine to have no survival benefit studied monotherapy.

In the metastatic setting, heterogeneity of trial design made specific robust conclusions more difficult. The benefit for hormone receptor-positive tumours relative to hormone receptor-negative cancers appeared to be driven by concurrent or sequential delivery of capecitabine with docetaxel, although further confirmatory trials would be ideal to validate this conclusion. Unfortunately, the higher toxicity of the capecitabine and docetaxel combination, particularly in a palliative setting, makes such further studies unlikely and application to practice inappropriate in many cases. As monotherapy is favoured in metastatic breast cancer over "doublet" chemotherapy regimens, it is unfortunate that only Study 301 compared capecitabine to another monotherapy regimen (eribulin).
In the neoadjuvant setting, where trials tend to be hypothesis-generating for validation in larger adjuvant studies, heterogeneity

of design, the tendency for multiple treatment arms to be studied within each trial, and small cohort sizes precluded useful conclusions as to hormone receptor subtype-specific activity of capecitabine in this scenario. Consequently, there is no evidence that capecitabine is beneficial in the neoadjuvant setting.

Unfortuately, a number of planned analyses were not possible due to lack of available data. These included comparison of breast cancer-specific survival in the adjuvant setting, outcomes within hormone receptor-positive and -negative subsets by HER2 status in all treatment scenarios, and capecitabine efficacy by line of treatment in the metastatic setting. This limitation could be overcome by access to individual patient data; however this was beyond the scope of our review.

Quality of the evidence

The robustness of conclusions differed between treatment scenarios; this difference was driven by both size and heterogeneity of studies conducted in each situation.

The most robust finding was the significant differential benefit between hormone receptor-positive and -negative cancers in the adjuvant setting, with substantial benefit derived from inclusion of capecitabine only for hormone receptor-negative and triple-negative disease - for both DFS and OS - with low heterogeneity (I^2 < 50% for all parameters). In this context, some doubt exists regarding the value of capecitabine added after completion of other chemotherapies, as studied in two trials totaling 1742 patients with high heterogeneity of outcome. Uncertainty arises from discrepancies between the outcomes of CIBOMA 2004-01 and CREATE-X, as discussed above. In contrast, remarkably consistent and substantial benefits are seen across the three trials studying the addition of capecitabine concurrently with docetaxel, with low heterogeneity in hormone receptor-negative and triple-negative cancers. Here 1669 hormone receptor-negative patients and 1543 triple-negative patients were treated across three trials of very similar design with very low heterogeneity for the OS outcome (I^2 = 0% for both hormone receptor-negative and triple-negative disease) (CBCSG-10; FINXX; USON 01062). Although no benefit was observed for hormone receptor-positive disease, the smaller number of studies and the greater heterogeneity in trial design of these studies do not exclude some level of benefit here.

In the metastatic setting, substantially greater variability of trial design and a wider range of alternative therapeutics were employed. The twelve eligible trials involving 4325 patients were broadly divisible into three designs with respect to capecitabine inclusion: four studies including 1783 patients, in which capecitabine monotherapy was compared to other treatments; four studies including 1145 patients, in which capecitabine was added to a regimen; and four trials involving 1397 patients, in which the drug was substituted for a component of a regimen. Given combined outcomes across all studies, although we saw significant PFS benefit for hormone receptor-positive tumours that was not observed for other tumours, it is worth noting that trial heterogeneity was high (I^2 = 81%), and that only 3 of the 12 trials studied contributed DFS and OS data for comparison of all subtypes, and 6 of the 12 for comparison of hormone receptor-positive and hormone receptor-negative disease. In light of the different trial designs regarding incorporation of capecitabine into the chemotherapy regimen, it should also be noted that only a proportion of studies in each category contributed to outcome measures by subtype, thereby reducing the robustness of derived conclusions.

For the neoadjuvant setting, six trials and 3152 participants were included. Study design heterogeneity prevented any robust conclusions with multiple agents compared to capecitabine. No hormone receptor-specific differences were seen for capecitabine incorporation, and lack of hormone receptor-specific DFS and OS data precluded validation of results seen in the adjuvant setting.

Potential biases in the review process

The capecitabine trials included in this review were invariably open-label with no blinded placebo control. This may have introduced bias into reporting of toxicity. However, the more critical endpoints of response rate, PFS, DFS, RFS, and OS are less likely to have been adversely affected by such open-label designs.

Several randomised controlled studies are awaiting peer-reviewed publication. Notably, CBCSG-10, which was one of three trials that demonstrated benefit of the addition of capecitabine for TNBC in the adjuvant setting, is yet to be published in a peer-reviewed journal. However, as previously discussed, the hazard ratio for OS in CBCSG-10 is similar to that of triple-negative subgroup analyses from both FINXX and USON 01062. Nonetheless there is the potential for reporting bias, with CBCSG-10 being a positive trial. Other trials as detailed in the Ongoing studies section of this review are pending peer-reviewed publication, including the TABEA study.

As with any collation of published studies relevant to a particular question in which the question is unlikely to have featured in pre-determined primary or secondary outcomes, there is potential for publication bias with respect to data regarding outcomes by hormone receptor status. Post-hoc analyses that did not show a significant difference may have been selectively omitted from published works relative to studies showing significant differential outcomes by hormone receptor status.

Agreements and disagreements with other studies or reviews

Other reviews in each of the three treatment scenarios explored herein have identified similar correlations to the work presented here.

In the metastatic setting, a relatively contemporary review of randomised trials incorporating capecitabine included ten studies totaling 2002 patients (Wang 2012). Again, comparable results were attained for whole cohorts undifferentiated by hormone receptor status, with studies finding modest non-significant increases in complete response rates for capecitabine inclusion with substantial heterogeneity. However, no analysis by hormone receptor status was made such that our own finding of superior complete response rates for capecitabine in hormone receptor-positive disease only was not tested. Further, no analysis of DFS or OS was made, thereby leaving our findings of superior outcomes in hormone receptor-positive but not in hormone receptor-negative patients again unreported. However, our findings are supported by a pooled analysis of individual patient data from capecitabine monotherapy clinical trials in metastatic breast cancer, where significantly improved response rates, PFS, and OS with capecitabine were demonstrated in patients with hormone receptor-positive versus hormone receptor-negative tumours (Blum 2012).

A very recent review of seven adjuvant studies, based solely on TNBC patients or reporting outcomes for TNBC subsets, found benefit for DFS (HR 0.77; P = 0.001) and for OS similar to our findings (HR 0.69; P = 0.001). Although the stated intent was to study the addition of capecitabine to standard chemotherapy, in fact two included negative studies substituted capecitabine for cyclophosphamide - GEICAM 2003-10 and Zhang 2015 - the latter of which has not been included in our analysis of studies adding capecitabine.

In contrast, a previous review, which studied the addition of capecitabine only in the adjuvant setting without a prospective subtype focus, incorporating 9302 patients in eight trials, found no overall effect of capecitabine on DFS or OS (Natori 2017), in keeping with the overall population in our study. These review authors observed that capecitabine appeared to exert a beneficial effect on DFS when added to a regimen in comparison to its effect when substituted for an existing component, although they did not demonstrate significant benefit of addition over standard treatment for any outcome measure. Further, they reported a significant beneficial effect on OS for the addition of capecitabine in trials with greater proportions of triple-negative cancers. However, an OS benefit specifically in triple-negative patients alone was not reported, potentially as the results of CBCSG-10 and CIBOMA 2004-01 were not available at the time of publication, and because they did not specifically extract patient cohorts by hormone receptor expression profile. In contrast, we found significant OS benefit for the whole cohort, as well as for hormone receptor-negative and triple-negative patients, from capecitabine addition, along with DFS benefit for hormone receptor-negative and triple-negative patients.

A review of capecitabine incorporation in the neoadjuvant setting included five trials totaling 3257 patients (Li 2013), four of which were included in our own review, which also included two newer studies. Findings were essentially identical to our own, showing no benefit for pCR from capecitabine inclusion on a background of significant heterogeneity. This study did not report DFS or OS, both of which we found to be unchanged by capecitabine addition.

Worthy of comment is the as yet unpublished meta-analysis of 15,457 individual patients from 12 neoadjuvant or adjuvant studies exploring the impact of capecitabine on outcomes that included assessment of results by receptor status, presented at the San Antonio Breast Cancer Symposium in 2019 (Mackelenbergh 2019). A core difference regarding this analysis relative to our study was the combination of adjuvant and neoadjuvant trial outcomes. We found that data in available publications of neoadjuvant trials were insufficient to enable their incorporation into useful DFS and OS analyses. Nevertheless, results were in close concordance with our own based on adjuvant patients alone, also concluding that benefits were largely confined to TNBC subsets, and were driven by the utility of capecitabine when added to a regimen rather than substituted.

OS benefits in this presented meta-analysis for capecitabine added to existing regimens in the TNBC population were more modest (HR 0.778; P = 0.004) than those observed in our own study (HR 0.61; P = 0.0004). This difference could be accounted for by inclusion of 345 neoadjuvant patients from the GeparQuattro study, for which no subtype-related outcome data were available for this negative study; by inclusion of 773 neoadjuvant patients from the NSABP-40 study, which added either capecitabine or gemcitabine to an existing regimen, which we therefore classified as a substitution study that also produced a negative result; and by exclusion of 561 patients from the CBCSG-10 study, which added capecitabine to docetaxel after anthracycline-based therapy, presumptively because of lack of individual patient data, yielding a positive result.

AUTHORS' CONCLUSIONS

Implications for practice

In metastatic disease, a signal for greater activity was seen for capecitabine in hormone receptor-positive cancers compared to no benefit for hormone receptor-negative cancers. However, the core driver of this result was the use of capecitabine in combination with docetaxel, where excess toxicity prevents widespread use. Overall, capecitabine as a single agent had comparable efficacy to other single agents, and so is a reasonable choice for all subtypes in this setting due to a relatively favourable toxicity profile.

Differential sensitivity of relevance to clinical practice was again observed in the adjuvant setting, albeit in the reverse direction. Although no significant benefit was observed for capecitabine inclusion in the hormone receptor-positive population, we identified statistically and clinically significant disease-free survival and overall survival benefits for the addition of capecitabine to docetaxel, when given sequentially either before or after an anthracycline-based component, in hormone receptor-negative or triple-negative breast cancer. Heterogeneity was very low despite involved studies carried out in racially diverse populations. Capecitabine inclusion should therefore be considered, at least in high-risk triple-negative cases, after surgery. When patients treated with standard neoadjuvant chemotherapy for triple-negative breast cancer have failed to achieve a pathological complete response, addition of capecitabine post surgery at a starting dose of 1250 mg/m^2 twice daily is warranted based on CREATE-X study outcomes, given that a corroborating trial in a more racially diverse population would strengthen the case for widespread application of these data.

Implications for research

The differential activity of capecitabine between hormone receptor-positive and -negative cancers in micro-metastatic and macro-metastatic settings could provide an opportunity to better understand the differential biology between these settings. The active moiety from capecitabine metabolism, 5-fluorouracil, was developed in the 1950s, thereby pre-dating knowledge of oestrogen receptor signalling in breast cancer cell lines, such that this differential sensitivity has not been established nor explored in vitro or in vivo.

Translational laboratory work exploring the differential impact of fluorouracil on dormant and cycling as well as hormone receptor-positive and -negative cell lines may yield biological insights to allow better selection of patients or to even improve sensitivity to fluorouracil-based treatments.

Demonstrated overall survival benefit of capecitabine in the adjuvant setting for triple-negative cancers warrants further investigation with additional randomised trials to confirm our findings. Pending such trials, consideration of capecitabine inclusion with docetaxel in high-risk triple-negative breast cancer patients adjuvantly appears justified. Internationally, the addition of platinum-based agents to adjuvant chemotherapy in triple-negative disease has gained considerable traction based on theoretically heightened sensitivity due to an increased incidence of DNA-repair deficits, as well as observations of increased pathological complete response rates with platinum agent inclusion in neoadjuvant studies. However, to date, confirmation of overall survival benefit has not been achieved. Further studies into the biology of triple-negative breast cancer are urgently required to assess the benefits of capecitabine, platinum, and anti-programmed cell death-1 immunotherapy. Our study suggests that capecitabine may have strong utility in the adjuvant setting for triple-negative breast cancer.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ABCSG-24

Study characteristics	
Methods	Accrual time: 2004 to 2008 Multi-centre: Austria Phase 3 open-label randomised controlled trial Median follow-up: not reported Baseline comparability: balanced
Participants	N = 536 females Age: range 25 to 73 years; median 49 years in both arms Diagnosis: invasive breast cancer (except T4d); scheduled to receive preoperative chemotherapy Inclusion criteria: females; aged 18 to 70 years with histologically proven, core-biopsied, invasive breast cancer (except T4d); scheduled to receive preoperative chemotherapy; World Health Organization (WHO) performance status ≤ 2; no distant disease; no prior/current neoplasm (except curatively treated non-melanoma skin cancer or in situ cervical cancer); adequate left ventricular ejection fraction (LVEF > 50% lower normal limit) 4 weeks before study medication Exclusion criteria: congestive heart failure or unstable angina pectoris; history of myocardial infarction within 1 year; uncontrolled hypertension/arrhythmias; neuropathy ≥ grade 2; preoperative local treatment of EBC or concurrent corticosteroid use (except when used for long-term treatment, initiated > 6 months before study entry, at low dose ≤ 20 mg methylprednisolone or equivalent, or as inhalational agents, for prophylaxis, treatment of acute hypersensitivity reactions, or nausea/vomiting) Notes: 45% had node-positive disease. 67% were hormone receptor-positive 23.3% were HER2-positive Triple-negative rate was not reported
Interventions	Neoadjuvant setting

ABCSG-24 *(Continued)*

	Arm 1 (EDC) (N = 270): epirubicin (75 mg/m^2 IV Day 1) plus docetaxel (75 mg/m^2 IV Day 1) plus capecitabine (1000 mg/m^2 twice daily oral Days 1 to 14) every 3 weeks for 6 cycles Arm 2 (ED) (N = 266): epirubicin (75 mg/m^2 IV Day 1) plus docetaxel (75 mg/m^2 IV Day 1) every 3 weeks for 6 cycles Other adjuvant therapies: patients with HER2-positive disease were further randomised to receive trastuzumab (8 mg/kg IV loading, then 6 mg/kg IV Day 1 every 3 weeks) or not. All patients received G-CSF
Outcomes	Primary: pathological complete response (absence of invasive tumour in the final surgical breast sample (stage yT0 or ypTis), according to local pathologist, irrespective of nodal status; specimens judged as pCR were reviewed by a central pathologist; all pathologists were blinded to treatment) Secondary: rate of axillary lymph node involvement at the time of surgery; rate of breast-conserving surgery
Identification	Trial registration link: https://clinicaltrials.gov/ct2/show/NCT00309556 Sponsorship source: Austrian Breast and Colorectal Cancer Study Group (ABCSG). Financial and logistical support from Amgen Austria, Roche Austria, Sanofi Aventis Austria, and EBEWE Austria **Author's name:** Guenther G. Steger **Institution:** Medical University of Vienna **Email:** guenther.steger@meduniwien.ac.at **Address:** Comprehensive Cancer Center and Department of Internal Medicine, Division of Oncology, Medical University of Vienna, Waehringer, Guertel 18–20, A-1090 Vienna, Austria
Notes	All randomised patients were included in intention-to-treat analysis Hormone receptor status not subdivided beyond HR-positive or -negative and not described separately in terms of characteristics

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised via computer programme with appropriate stratification factors
Allocation concealment (selection bias)	Low risk	Centralised randomisation with presumed allocation concealment but no explicit comment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study with no placebo
Blinding of outcome assessment (detection bias) Pathologic complete response (pCR) - neoadjuvant studies only	Low risk	Primary outcome of pCR centrally confirmed by pathologist who was blinded to treatment arm
Blinding of outcome assessment (detection bias) Toxicities	High risk	Given unblinded study, high risk due to difference in toxicity profile

ABCSG-24 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Adequate reporting of pre-specified primary and secondary endpoints; all patients included in ITT analysis
Selective reporting (reporting bias)	High risk	Adverse event reporting very broad. No specific documentation of common AEs such as febrile neutropenia, neutropenia, anaemia, diarrhoea, and so forth. pCR of TNBC was not a pre-specified analysis. pCR of non-TNBC excluded patients with HER2-positive breast cancer who received trastuzumab. Reporting of pCR non-TNBC patients is therefore incomplete. Trial definition of pCR of breast and nodes is not pre-specified
Other bias	Unclear risk	Overall survival; relapse-free survival was not a secondary endpoint

BOLERO6

Study characteristics	
Methods	Accrual time: March 2013 to November 2014 Multi-centre: 83 centres across 18 countries Phase 2 open-label randomised controlled trial Median follow-up: 37.6 months Baseline comparability: A larger proportion of patients in the capecitabine arm vs the everolimus plus exemestane and everolimus alone arms were white (n = 91 vs n = 78 and n = 85, respectively), younger than 65 years (n = 69 vs n = 65 and n = 64), had ECOG performance status of 0 (n = 57 vs n = 54 and n = 48), or had bone-only metastases (n = 24 vs n = 13 and n = 16), and fewer patients in the capecitabine arm had ≥ 3 metastatic sites (n = 45 vs n = 52 and n = 47)
Participants	N = 309 women Age: median 61 years (range 32 to 88) Diagnosis: ER-positive, HER2-negative metastatic or recurrent breast cancer Inclusion criteria: post-menopausal women with ER-positive, HER2-negative metastatic or recurrent breast cancer that had recurred or progressed during treatment with letrozole or anastrozole; ECOG performance status 0 to 2; adequate bone marrow, coagulation, liver, and renal function; fasting serum cholesterol ≤ 300 mg/dL; fasting triglycerides ≤ 2.5 × upper limit of normal Exclusion criteria: prior treatment with strong inhibitors or inducers of isoenzyme cytochrome P450-3A for ≥ 7 days within 2 weeks of randomisation, or treatment with sorivudine or any of its chemically related analogues within 4 weeks of randomisation; another malignancy within 5 years of randomisation (except adequately treated in situ carcinoma of the cervix uteri, basal or squamous cell carcinoma, non-melanomatous skin cancer, or history of stage IA melanoma that has been cured), or current or historical central nervous system metastases; radiotherapy within 4 weeks of randomisation, unless localised palliative radiotherapy, or radiotherapy for lytic lesions at risk of fracture completed ≥ 2 weeks before randomisation; hormone replacement therapy that was not discontinued before randomisation; known history of HIV; severe and/or uncontrolled medical condition; bilateral diffuse lymphangitis; active bleeding diathesis Note: Entire cohort ER-positive
Interventions	Metastatic ARM 1 (exemestane + everolimus): N = 104 Everolimus 10 mg/d orally plus oral exemestane 25 mg daily continuously until progression or intolerance ARM 2 (everolimus): N = 103 Everolimus 10 mg/d orally continuously until progression or intolerance ARM 3 (capecitabine): N = 102

BOLERO6 *(Continued)*

	Capecitabine 1250 mg/m^2 twice daily for 14 days of a 21-day cycle for as many cycles until progression or intolerance
Outcomes	Primary: progression-free survival for everolimus plus exemestane vs everolimus Secondary: progression-free survival for everolimus plus exemestane vs capecitabine; safety; overall survival
Identification	Trial registration link: https://clinicaltrials.gov/ct2/show/NCT01783444 Funding considerations: Novartis **Author's name:** Guy Jerusalem **Institution:** Department of Medical Oncology, CHU Sart Tilman Liege, Liege University, Domaine Universitaire du Sart Tilman, B35, 4000 Liege, Belgium **Email:** g.jerusalem@chu.ulg.ac.be
Notes	All randomised patients were included in intention-to-treat analysis Hazard ratios were inverted from published data Interim analysis was performed after 75 PFS events and it was deemed safe to proceed on to conclusion of study Although there were 3 arms in the study, outcomes were reported via ARM1 vs ARM2 and ARM1 vs ARM3. Only the results for ARM1 vs ARM3 were relevant to this analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Interactive response technology (IRT) was used to randomise eligible patients in a 1:1:1 ratio to 1 of the 3 treatment arms, with randomisation stratified by the presence or absence of visceral disease. Randomisation was performed with a block size of 6 to ensure 1:1:1 randomisation within the strata
Allocation concealment (selection bias)	Low risk	A subject randomisation list, produced by Novartis, was provided by the IRT provider using a validated system that automated random assignment of subject numbers to randomisation numbers. These randomisation numbers were linked to the different treatment arms, which in turn were linked to medication numbers by a validated system that automated the random assignment of medication numbers to packs containing study treatment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) Overall survival	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Progression-free survival (PFS)	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, assessed at high risk of bias because outcome can be subjective
Blinding of outcome assessment (detection bias) Overall response rate (ORR)	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, assessed to be at high risk of bias because outcome can be subjective
Blinding of outcome assessment (detection bias)	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, assessed to be at high risk of bias because outcome can be subjective

BOLERO6 *(Continued)*

Clinical benefit rate		
Blinding of outcome assessment (detection bias) Toxicities	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, high risk due to difference in toxicity profile
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited patients accounted for at each stage of analysis and included in ITT analysis. Attrition thoroughly reported
Selective reporting (reporting bias)	Low risk	Adequate reporting of pre-specified primary and secondary endpoints
Other bias	Low risk	No other sources of bias detected

CBCSG-10

Study characteristics	
Methods	Accrual time: June 2012 to November 2013 Multi-centre: China (35 sites) Phase 3 open-label randomised controlled trial Median follow-up: 30 months Baseline comparability: balanced
Participants	N = 636 females Age: average 49.07 years in capecitabine arm; 48.3 years in comparator arm Diagnosis: invasive triple-negative breast cancer Inclusion criteria: Exclusion criteria: T stage > T4a; ER-, PR-, or HER2-positive disease Notes: 34.6% had node-positive disease 100% had triple-negative disease
Interventions	Adjuvant setting ARM 1 (TX-XEC): (N = 288) docetaxel (75 mg/m² IV Day 1) plus capecitabine (1000 mg/m² twice daily oral Days 1 to 14) every 3 weeks for 3 cycles followed by epirubicin (75 mg/m² IV Day 1) plus cyclophosphamide (500 mg/m² IV Day 1) plus capecitabine (1000 mg/m² twice daily oral Days 1 to 14) every 3 weeks for 3 cycles ARM 2 (T-FEC): (N = 273) docetaxel (75 mg/m² IV Day 1) every 3 weeks for 3 cycles followed by 5-FU (500 mg/m² IV Day 1) plus epirubicin (75 mg/m² IV Day 1) plus cyclophosphamide (500 mg/m² IV Day 1) every 3 weeks for 3 cycles Co-interventions were not reported
Outcomes	Primary: 5-year disease-free survival (including local relapse, distant metastasis, contralateral breast cancer, second primary cancer, or death from any cause)

CBCSG-10 *(Continued)*

	Secondary: safety; quality of life at baseline, Week 9, and Week 18 (FACT-B scale); 5-year relapse-free survival and distant disease-free survival (measured from surgery to relapse); 5-year overall survival
Identification	Trial registration link: https://clinicaltrials.gov/ct2/show/NCT01642771 Funding considerations: funded by China Breast Cancer Clinical Study Group. No pharmaceutical funding declared
Notes	Not all randomised patients were included in intention-to-treat analysis Dose of fluorouracil was deemed different enough from capecitabine to be included in this study, despite the similarity between drug analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised 1:1 by central patient screening and randomisation system
Allocation concealment (selection bias)	Low risk	Centralised randomisation with presumed allocation concealment but no explicit comment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) Recurrence-free survival (RFS)	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Disease-free survival (DFS)	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Toxicities	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, high risk due to difference in toxicity profile
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data not fully published
Selective reporting (reporting bias)	Unclear risk	Data not fully published
Other bias	Unclear risk	Unclear risk, as the impact of both arms containing a 5-FU compound is unclear The main difference between arms is the duration and delivery of 5-FU

Chan 2009

Study characteristics

Chan 2009 *(Continued)*

Methods	Accrual time: October 2002 to March 2004 Multi-centre: United Kingdom, France, Germany, Italy, Spain, Denmark (49 sites) Phase 3 open-label randomised controlled trial Median follow-up: not reported Baseline comparability: balanced
Participants	N = 305 females Age: median 53 years (range 30 to 78) in capecitabine arm; 56 years (range 26 to 76) in comparator arm Diagnosis: locally advanced or metastatic breast cancer Inclusion criteria: age ≥ 18 years; histological or cytological diagnosis of locally advanced or metastatic breast cancer; measurable disease per RECIST; Karnofsky performance status ≥ 70; adequate bone marrow, liver, and renal function; estimated life expectancy ≥ 12 weeks; treatment with 1 prior anthracycline regimen (neo/adjuvant or first-line metastatic setting); taxane pretreatment permitted in the neo/adjuvant setting if completed ≥ 6 months before enrolment; hormonal therapy or immunotherapy terminated before enrolment; prior radiation therapy permitted if < 25% of bone marrow was treated, and if treatment was completed ≥ 4 weeks before enrolment Exclusion criteria: inflammatory breast disease; brain metastasis; second primary malignancy; serious concomitant illness; peripheral neuropathy ≥ grade 2; cardiac abnormalities Notes: 70.5% were hormone receptor-positive 17% were HER2-positive Triple-negative rate was not reported
Interventions	First- or second-line metastatic setting ARM 1 (CD): (N = 152) docetaxel (75 mg/m^2 IV Day 1) plus capecitabine (1250 mg/m^2 twice daily orally Days 1 to 14) every 3 weeks ARM 2 (GD): (N = 153) docetaxel (75 mg/m^2 IV Day 1) plus gemcitabine (1000 mg/m^2 Day 1 and Day 8) every 3 weeks
Outcomes	Primary: progression-free survival (time from date of random assignment to first date of documented progression or death from any cause) Secondary: overall survival (time from date of random assignment to date of death from any cause); overall response rate; time to treatment failure (time from date of random assignment to date of first of the following events: discontinuation, progressive disease, death from any cause, or the start of a new anticancer therapy); toxicity; quality of life
Identification	Trials registration link: https://clinicaltrials.gov/ct2/show/NCT00191438 Funding considerations: supported by Eli Lilly **Author's name:** Stephen Chan **Institution:** Nottingham University Hospital **Email:** steve.chan@nuh.nhs.uk **Address:** Nottingham University Hospital, City Campus, Hucknall Road, Nottingham NG5 United Kingdom

Chan 2009 *(Continued)*

Notes	All randomised patients were included in the intention-to-treat analysis Hazard ratios for OS were calculated with the RevMan calculator All other hazard ratios were inverted from published data No efficacy data by ER/hormone receptor status were reported in original publication, but these data were published in subsequent pooled analysis (Seidman 2014)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	No description of randomisation method, but large multi-centre trial; presumed to use reasonable randomisation methods
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study with no placebo
Blinding of outcome assessment (detection bias) Overall survival	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Progression-free survival (PFS)	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, assessed to be at high risk of bias because outcome can be subjective
Blinding of outcome assessment (detection bias) Overall response rate (ORR)	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, ORR assessed to be at high risk of bias because outcome can be subjective
Blinding of outcome assessment (detection bias) Toxicities	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, high risk due to difference in toxicity profile
Blinding of outcome assessment (detection bias) Quality of life (QoL) - metastatic studies only	Unclear risk	Given the heterogeneity of treatment arms, both with clear pros and cons for quality of life. As this was an unblinded study and that this outcome is subjective, study deemed to be at unclear risk
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited patients accounted for at each stage of analysis and included in ITT analysis
Selective reporting (reporting bias)	Unclear risk	Unclear risk, as it is unclear whether the earlier analysis was pre-planned Outcomes by hormone status not pre-planned and reported only in pooled analysis
Other bias	Unclear risk	Pooled analysis performed with Seidman 2011 No other sources of bias detected

CHAT

Study characteristics	
Methods	Accrual time: February 2002 to September 2005 Multi-centre: UK, Mexico, Brazil, Costa Rica, Poland, Australia, Spain (43 centres) Phase 2 randomised open-label controlled trial Median follow-up: 25.9 months capecitabine arm; 23.5 months comparator arm Baseline comparability: capecitabine arm with higher proportion of hormone receptor–positive tumours (50.0% vs 40.9%) and longer median duration of primary disease to diagnosis of metastasis (16.5 vs 10.1 months)
Participants	N = 222 females Age: median 53 years (range 24 to 82) in capecitabine arm; 52 years (range 23 to 78) in comparator arm Diagnosis: locally advanced or metastatic HER2-positive invasive breast cancer Inclusion criteria: women age ≥ 18 years; HER2-positive (immunohistochemistry 3+ or fluorescence in situ hybridisation–amplified; ratio HER2:chromosome 17 ≥ 2); inoperable locally advanced or metastatic breast cancer; RECIST measurable disease; baseline LVEF ≥ 50%; ECOG 0 to 2 (later amended to 0 to 1); no history of significant cardiac disease, congestive heart failure, angina, hypertension, heart valve disease, arrhythmias, or transmural infarction detected by ECG Exclusion criteria: previous chemotherapy for locally advanced or metastatic disease; previous anti-HER2 therapy, docetaxel, paclitaxel, capecitabine, or infusional fluorouracil Notes: 50% in capecitabine arm and 40.9% in comparator arm had hormone receptor-positive disease 100% in both arms were HER2-positive
Interventions	First-line metastatic setting ARM 1 (HTX): (N = 112) trastuzumab (8 mg/kg IV loading dose cycle 1, then 6 mg/kg IV Day 1 from cycle 2 onwards) plus docetaxel (75 mg/m^2 IV Day 1) plus capecitabine (950 mg/m^2 twice daily oral Days 1 to 14) every 3 weeks ARM 2 (HT): (N = 110) trastuzumab (8 mg/kg IV loading dose cycle 1, then 6 mg/kg IV Day 1 from cycle 2 onwards) plus docetaxel (100 mg/m^2 IV Day 1) every 3 weeks Other adjuvant therapies: concomitant hormone treatment not allowed G-CSF allowed if febrile neutropenia, neutrophils < 1.5 × 10^9/L for > 1 week, or 2 dose delays of docetaxel Note: higher dose of docetaxel in comparator arm (100 mg/m^2 vs 75 mg/m^2)
Outcomes	Primary: overall response rate (complete or partial response by RECIST) Secondary: progression-free survival (disease progression or death); time to progression (disease progression, not death); overall survival (death from any cause); safety; time to response (from randomisation to first documentation of complete response or partial response); duration of response (from first documented response to disease progression, death, or withdrawal)
Identification	Trial registration link: not available

CHAT *(Continued)*

	Funding considerations: F. Hoffmann-La Roche Ltd, Basel, Switzerland. All drug and dispensing costs for trastuzumab, docetaxel, and capecitabine within this trial were funded by the sponsor. Investigator, research nurse, and data management were also funded by the sponsor **Author's name:** Andrew Wardley **Institution:** The Christie **Email:** andrew.wardley@christie.nhs.uk **Address:** Cancer Research UK Department of Medical Oncology, The Christie, 550 Wilmslow Rd, Manchester M20 4BX United Kingdom
Notes	Not all randomised patients were included in intention-to-treat analysis. Only patients who received ≥ 1 dose of drug were included in statistical analysis Post-hoc unplanned exploratory analyses of ORR and PFS by ER status

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	No description of method of randomisation in text, but large multi-centre trial; presumed to use reasonable randomisation methods
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) Overall survival	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Progression-free survival (PFS)	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, assessed to be at high risk of bias because outcome can be subjective
Blinding of outcome assessment (detection bias) Overall response rate (ORR)	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, assessed to be at high risk of bias because outcome can be subjective
Blinding of outcome assessment (detection bias) Toxicities	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, high risk due to difference in toxicity profile
Incomplete outcome data (attrition bias) All outcomes	High risk	Not all patients included in ITT analysis
Selective reporting (reporting bias)	Unclear risk	Data not mature, so unclear
Other bias	Low risk	No other sources of bias detected

CIBOMA 2004-01

Study characteristics	
Methods	Accrual time: 26 October 2006 to 12 September 2011 Multi-centre: 8 countries, 80 sites Phase 3 international open-label randomised study Median follow-up: not reported Baseline comparability: marginally more stage III disease in capecitabine arm (n = 106 (23.7%) vs n = 80 (18.7%)) and more stage I and II in the observation arm (stage I – n = 62 (13.8%) vs n = 74 (17.3%), stage II – n = 270 (60.3%) vs n = 271 (63.3%)); this was also reflected in the surgery (ALND yes/no, more in capecitabine arm). Marginally more patients in the capecitabine arm were receiving neoadjuvant (n = 89 19.9% vs n = 75 (17.5%)), and more patients in the observation arm received adjuvant only (n = 353 (78.8%) vs n = 352 (82.2%)
Participants	N = 876 Age: capecitabine 50 years (20 to 79); observation 49 (23 to 82) Diagnosis: triple-negative breast cancer following standard neo/adjuvant chemotherapy and surgery Inclusion criteria: centrally confirmed triple-negative disease, T1c to T3, N0 to N3a, M0; prior standard neo/adjuvant chemotherapy with anthracyclines ± taxanes; 6 cycles of standard chemotherapy mandatory except for N0 tumours (4 cycles of anthracycline-based chemotherapy acceptable); surgery with free margins Exclusion criteria: not reported Notes: Entire cohort was triple-negative Randomisation was stratified by institution, basal phenotype (by CK 5/6, EGFR staining), ALN 0 vs 1 to 3 vs > 4) and prior chemotherapy (anthracyclines vs anthracyclines + taxanes)
Interventions	Adjuvant ARM 1 (capecitabine): N = 448 capecitabine 1000 mg/m^2 taken orally twice daily for 14 days of a 21-day cycle, for 8 cycles ARM 2 (observation): N = 428 Note: Median dose intensity achieved – 86.3%
Outcomes	Primary: disease-free survival for intention-to-treat population Secondary: overall survival, subgroup analyses; safety; biomarkers
Identification	Trial registration link: https://clinicaltrials.gov/ct2/show/NCT00130533 Funding considerations/Collaborators: Hoffmann-La Roche; IBEROAMERICAN COALITION FOR BREAST ONCOLOGY RESEARCH (CIBOMA); Spanish Breast Cancer Research Group **Author's name:** C.H. Barrios **Institution:** H Sao Lucas de PUCRS, Medical Oncology, Porto Alegre, Brazil
Notes	All randomised patients were included in intention-to-treat analysis Outcomes were available only via conference slides and abstract; publication was not available at time of review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation 1:1. No explicit description of method of randomisation in conference slides, but large multi-centre trial; presumed to use reasonable randomisation methods

CIBOMA 2004-01 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No explicit description of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) Overall survival	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Disease-free survival (DFS)	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Toxicities	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, high risk due to difference in toxicity profile
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Discussion of number randomised. No description of number screened, nor of attrition rates or reasons for attrition. Results thus far available only in conference slides and abstract
Selective reporting (reporting bias)	Low risk	Complete reporting of pre-specified primary and secondary outcomes
Other bias	Unclear risk	Not yet fully reported, thus consensus was that this is unclear; no overt other sources of bias identified

CREATE-X

Study characteristics	
Methods	Accrual time: February 2007 to July 2012 Multi-centre: Korea and Japan Phase 3 randomised controlled trial Median follow-up: 3.6 years Baseline comparability: balanced
Participants	N = 910 females Age: median 48 years (range 25 to 74) in both arms Diagnosis: HER2-negative invasive breast cancer requiring neoadjuvant chemotherapy Inclusion criteria: HER2 negative breast cancer stage I-IIIB and pathologically assessed residual disease after neoadjuvant chemotherapy with anthracycline, taxane or both. Age 20-74 and ECOG 0-1. Exclusion criteria: HER2-positive disease; pathological complete response and negative nodes after neoadjuvant chemotherapy Notes: 61% had node-positive disease

CREATE-X *(Continued)*

	63.4% were hormone receptor-positive 0% were HER2-positive 33.4% had triple-negative disease
Interventions	Adjuvant setting in patients who had already received neoadjuvant chemotherapy. All patients received neoadjuvant chemotherapy (physician's choice but not containing 5-FU or capecitabine). If surgical specimen revealed incomplete pathological response or positive lymph nodes, then patients were randomised ARM 1 (capecitabine): (N = 440) capecitabine (1250 mg/m^2 twice daily oral Days 1 to 14) every 3 weeks for 8 cycles (first 50 patients received 6 cycles, but after first safety analysis, this was extended to 8 cycles) ARM 2 (no chemotherapy): (N = 445) Other adjuvant therapies: hormone therapy was given to hormone receptor-positive patients. Of hormone receptor-positive patients randomised to the capecitabine arm, some received hormone therapy concurrently (200/275) and some started hormone therapy after chemotherapy (24/275) (unclear whether or when the other 51 patients received hormone treatment) Other co-interventions were not reported
Outcomes	Primary: disease-free survival Secondary: overall survival; time from first day of preoperative chemotherapy to recurrence or death; safety; cost-effectiveness
Identification	Trial registration link: UMIN000000843 Funding considerations: funded by ACRO (Advanced Clinical Research Organization) and JBCRG (Japan Breast Cancer Research Group)
Notes	All randomised patients were included in intention-to-treat analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised 1:1 at central data centre with the use of concealed assignments and use of a minimisation method with appropriate stratification factors
Allocation concealment (selection bias)	Low risk	Centralised randomisation with presumed allocation concealment but no explicit comment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) Overall survival	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Disease-free survival (DFS)	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias)	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, high risk due to difference in toxicity profile

CREATE-X *(Continued)*

Toxicities		
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited patients accounted for at each stage of analysis..All randomised patients included in intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Adequate reporting of pre-specified primary and secondary endpoints
Other bias	Unclear risk	Study excludes patients who achieve pCR from neoadjuvant chemotherapy, thus selecting patients with potentially worse prognosis Additionally, in the TNBC cohort, the design compares capecitabine vs nothing, whereas in the HR+ cohort, the design compares capecitabine + AI/tamoxifen vs AI/tamoxifen. Consensus was that this may potentially cause bias towards the study arm in the TNBC cohort These factors could potentially affect DFS outcomes

Fan 2013

Study characteristics	
Methods	Accrual time: not reported Single-centre: China Phase 2 open-label randomised controlled trial Median follow-up: 24 months Baseline comparability: more visceral metastases in capecitabine arm (73% vs 59%) and fewer grade 3 tumours in capecitabine arm (15% vs 48%)
Participants	N = 53 females Age: median 49 years (range 27 to 71) in capecitabine arm; 48 years (range 32 to 67) in comparator arm Diagnosis: unresectable locally advanced or metastatic triple-negative breast cancer Inclusion criteria: age ≥ 18 years; histologically confirmed ER-negative, PR-negative, and HER2-negative primary breast cancer (ER- and PR-negative first defined as < 10% positive tumour cells with nuclear staining in IHC, then < 1% after April 2010; HER2-negative was IHC scoring 0 or 1+ or FISH non-amplified as per ASCO guidelines); ≥ 1 measurable lesion by RECIST 1.0; no prior treatment for advanced disease; anthracyclines given in neoadjuvant or adjuvant setting; ECOG ≤ 1; adequate organ function; previous paclitaxel allowed Exclusion criteria: primary tumour or relapse positive for ER, PR, or HER2; previous treatment for advanced disease; previous platinum or docetaxel Notes: 100% was triple-negative disease
Interventions	First-line metastatic setting ARM 1 (TX): (N = 26) docetaxel (75 mg/m^2 IV Day 1) plus capecitabine (1000 mg/m^2 twice daily oral Days 1 to 14) every 3 weeks for up to 6 cycles

Fan 2013 *(Continued)*

	ARM 2 (TP): (N = 27) docetaxel (75 mg/m² IV Day 1) plus cisplatin (75 mg/m² IV Day 1) every 3 weeks for up to 6 cycles
Outcomes	Primary: objective response rate (RECIST 1.0 criteria) Secondary: progression-free survival; overall survival; safety
Identification	Trial registration link: https://clinicaltrials.gov/ct2/show/NCT01928680 Funding considerations: AVON® China breast cancer research grant and National Natural Science Foundation of China **Author's name:** Fan, Y **Institution:** Cancer Institute and Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College **Email:** xubinghe@medmail.com.cn **Address:** No. 17, Panjiayuan Nanli, Chaoyang District, Beijing 100021 China
Notes	All randomised patients were included in intention-to-treat analysis Hazard ratios were inverted from published data

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	No explicit discussion with regards to randomisation process
Allocation concealment (selection bias)	High risk	Single-centre study; small numbers; no sequence allocation described; higher chance of poor concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) Overall survival	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Progression-free survival (PFS)	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, assessed to be at high risk of bias because outcome can be subjective
Blinding of outcome assessment (detection bias) Overall response rate (ORR)	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, assessed to be at high risk of bias because outcome can be subjective
Blinding of outcome assessment (detection bias) Clinical benefit rate	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, assessed to be at high risk of bias because outcome can be subjective
Blinding of outcome assessment (detection bias)	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, high risk due to difference in toxicity profile

Fan 2013 *(Continued)*

Toxicities		
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited patients accounted for at each stage of analysis and included in ITT analysis
Selective reporting (reporting bias)	Low risk	Adequate reporting of pre-specified primary and secondary endpoints
Other bias	Low risk	No other sources of bias detected

FINXX

Study characteristics	
Methods	Accrual time: 27 January 2004 to 29 May 2007. Multi-centre:Finland and Sweden Phase 3 open-label randomised controlled trial Median follow-up: 10.3 years Baseline comparability: balanced
Participants	N = 1500 females Age: median 52 years (range 26 to 65) in capecitabine arm and 53 years (27 to 65) in comparator arm Diagnosis: Invasive breast cancer Inclusion criteria: histologically confirmed invasive breast cancer with regional lymph nodes containing cancer (isolated tumour cells < 0.2 mm in diameter were not considered metastases) or node-negative cancer with primary tumour diameter > 20 mm and PR-negative defined as staining < 10% of cancer cells on IHC; age 18 to 65 years; WHO performance status < 2; time interval between surgery and random assignment < 12 weeks; adequate hepatic, renal, and cardiac function Exclusion criteria: distant metastases or node-negative mucinous, papillary, medullary, or tubular cancer; received neoadjuvant chemotherapy Notes: 89.5% were node-positive 76.4% were ER-positive 62.3% were PR-positive 19% were HER2-positive Triple-negative rate was not reported
Interventions	Adjuvant setting ARM 1 (TX/XEC): (N = 753) docetaxel (60 mg/m^2 IV Day 1) plus capecitabine (900 mg/m^2 twice daily oral Days 1 to 14 every 3 weeks for 3 cycles followed by cyclophosphamide (600 mg/m^2 IV Day 1) plus epirubicin (75 mg/m^2 IV Day 1) plus capecitabine (900 mg/m^2 twice daily oral Days 1 to 14) every 3 weeks for 3 cycles

FINXX *(Continued)*

	ARM 2 (T/FEC): (N = 747) docetaxel (80 mg/m² IV Day 1) every 3 weeks for 3 cycles followed by cyclophosphamide (600 mg/m² IV Day 1) plus epirubicin (75 mg/m² IV Day 1) plus 5-FU (600 mg/m² IV Day 1) every 3 weeks for 3 cycles Notes: Lower dose of docetaxel was used in capecitabine arm (60 mg/m² vs 80 mg/m²) Growth factor support was not scheduled
Outcomes	Primary: relapse-free survival (time from random assignment to date of diagnosis of invasive breast cancer recurrence (local or distant) or death if patient died before recurrence; contralateral breast cancer or second malignancy not included) Secondary: safety; overall survival (time from random assignment to death)
Identification	Trial registration link: https://clinicaltrials.gov/ct2/show/NCT00114816 Funding: Roche, Sanofi-Aventis, AstraZeneca, Cancer Society of Finland; sponsored by the Finnish Breast Cancer Group **Author's name:** Heikki Joensuu **Institution:** Helsinki University Central Hospital **Email:** heikki.joensuu@hus.fi **Address:** Department of Oncology, Helsinki University Central Hospital, Haart-maninkaru 4, PO Box 180, FIN-00029 Helsinki, Finland
Notes	All randomised patients were included in intention-to-treat analysis Dose of 5-fluorouracil was deemed to be different enough from capecitabine to be included in this study despite the similarity between drugs Some hazard ratios were calculated with the RevMan calculator

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised in a 1:1 ratio. Assignment was central and was computer-assisted using permutated blocks with random block sizes. Stratification variables were appropriate
Allocation concealment (selection bias)	Low risk	Centralised randomisation with presumed allocation concealment but no explicit comment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) Overall survival	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Recurrence-free survival (RFS)	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding

FINXX *(Continued)*

Blinding of outcome assessment (detection bias) Disease-free survival (DFS)	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Breast cancer-specific survival	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Toxicities	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, high risk due to difference in toxicity profile
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited patients accounted for at each stage of analysis and included in ITT analysis
Selective reporting (reporting bias)	Low risk	Primary endpoint of RFS reported adequately, together with pre-specified subgroups, as well as DFS
Other bias	Low risk	No other sources of bias detected

GEICAM 2003-10

Study characteristics	
Methods	Accrual time: February 2004 to February 2007 Multi-centre: Spain (58 centres) Phase 3 open-label randomised controlled trial Median follow-up: 6.6 years. Baseline comparability: balanced
Participants	N = 1384 females Age: median 51 years (range 25 to 73) Diagnosis: invasive breast cancer Inclusion criteria: T1 to 3 N1 to 3 operable breast cancer; age 18 to 70 years; HER2-negative (after amendment); axillary nodal involvement; Karnofsky > 80; adequate bone marrow, renal, cardiac, and hepatic function Exclusion criteria: pN1b and c, pN2b, or pN3b and c disease (according to American Joint Committee of Cancer 2002 staging); HER2-positive disease initially included and subsequently excluded after amendment in October 2005; previous or concomitant systemic or radiation therapy for breast cancer; previous anthracyclines or taxanes; pre-existing neurotoxicity ≥ grade 2 according to National Cancer Institute Common Toxicity Criteria version 2.0; long-term therapy with corticosteroids; any other serious concomitant disorder or previous history of any malignancy other than adequately treated cervical or non-melanoma skin cancer or other cancers treated less than 10 years before study enrolment Notes: 100% had node-positive disease (note pN1b and c, pN2b, and pN3b and c were excluded from the study)

GEICAM 2003-10 *(Continued)*

	84.2% were hormone receptor-positive 10.3% were HER2-positive (enrolled before protocol amendment) 12% were triple-negative
Interventions	Adjuvant setting ARM 1 (ET-X): (N = 715) epirubicin (90 mg/m² IV Day 1) plus docetaxel (75 mg/m² IV Day 1) every 3 weeks for 4 cycles followed by capecitabine (1250 mg/m² twice daily oral Days 1 to 14) every 3 weeks for 4 cycles ARM 2 (EC-T): (N = 669) epirubicin (90 mg/m² IV Day 1) plus cyclophosphamide (600 mg/m² IV Day 1) every 3 weeks for 4 cycles followed by docetaxel (100 mg/m² IV Day 1) every 3 weeks for 4 cycles Notes: Lower dose of docetaxel was used in capecitabine arm (75 mg/m² vs 100 mg/m²) and no cyclophosphamide was given in capecitabine arm Both arms received G-CSF as primary prophylaxis for docetaxel-induced febrile neutropenia
Outcomes	Primary: invasive disease-free survival (time from date of random assignment to date of local or regional invasive breast cancer recurrence, distant recurrence, a second primary malignancy, or death from any cause, whichever occurred first) Secondary: overall survival (time between date of random assignment and death from any cause); safety (including an alopecia-specific study)
Identification	Trial registration link: https://clinicaltrials.gov/ct2/show/NCT00129935 Funding considerations: Spanish Breast Cancer Research Group, Sanofi, Hoffmann-La Roche, Pfizer **Author's name:** Miguel Martin **Institution:** Spanish Breast Cancer Research Group (GEICAM) **Email:** mmartin@ geicam.org **Address:** Instituto de Investigación Sanitaria Gregorio Marañón, Universidad Complutense, Dr Esquerdo 46, Madrid 28009, Spain
Notes	All randomised patients were included in intention-to-treat analysis Some hazard ratios were calculated with the RevMan calculator (see analyses)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised 1:1, centralised at the GEICAM HQ at Spanish Breast Cancer Group; appropriate stratification
Allocation concealment (selection bias)	Low risk	Centralised randomisation with presumed allocation concealment but no explicit comment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study

GEICAM 2003-10 *(Continued)*

Blinding of outcome assessment (detection bias) Overall survival	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Disease-free survival (DFS)	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Toxicities	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, high risk due to difference in toxicity profile
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited patients accounted for at each stage of analysis and included in ITT analysis
Selective reporting (reporting bias)	Low risk	Adequate reporting of pre-specified primary and secondary endpoints
Other bias	Low risk	No other sources of bias detected

GeparQuattro

Study characteristics	
Methods	Accrual time: August 2005 to December 2006 Multi-centre: Germany Phase 3 open-label randomised controlled trial Median follow-up: 5.4 years Baseline comparability: more lobular carcinoma in T-X group (13.8% vs 9.1% and 11%); more patients aged 40 to 49 in EC-T group
Participants	N = 1421 females Age: median 51 years (range 23 to 78) EC-TX arm, 50 (23 to 77) EC-T-X arm, 49 (22 to 75) EC-T arm Diagnosis: invasive breast cancer requiring neoadjuvant chemotherapy Inclusion criteria: histologically confirmed, previously untreated, unilateral or bilateral primary breast carcinoma; palpable tumour lesion ≥ 2cm or sonographic size ≥ 1 cm in diameter and measurable in 2 dimensions, preferably by sonography; all stages of disease in which adjuvant chemotherapy would be considered were eligible (e.g., locally advanced tumour with cT4 or cT3 stage; triple–negative tumour; ER- or PR-positive tumour that was cN-positive (for cT2) or pNSLN–positive (for cT1); age ≥ 18 years; Karnofsky performance status ≥ 80%; estimated life expectancy > 10 years disregarding the diagnosis of cancer; normal cardiac function confirmed by ECG and cardiac ultrasound (LVEF ≥ 55%); no evidence of distant disease (by bone scan, chest X-ray, and abdominal ultrasound and/or computed tomography (CT) scan); adequate bone marrow, renal, and liver function Exclusion criteria: tumour progression at time of ultrasound assessment during final week of fourth cycle of EC discontinued treatment and were not randomised; prior chemotherapy or radiotherapy for any malignancy; pregnancy or lactation; pre-existing motor or sensory neuropathy of severity ≥ grade 2 by National Cancer Institute (NCI) criteria; previous non-melanomatous malignant disease with disease-free survival < 5 years; known or suspected congestive heart failure (NYHA Class I) and/or coronary heart disease; history of myocardial infarction, uncontrolled arterial hypertension (i.e., blood pressure

GeparQuattro *(Continued)*

	> 160/90 mmHg under treatment with 2 antihypertensive drugs), or rhythm abnormalities requiring permanent treatment; history of significant neurological or psychiatric disorder; current active infection; active peptic ulcer; unstable or insulin-dependent type 2 diabetes mellitus; inadequate general condition; definite contraindications for use of corticosteroids; concurrent treatment with sex hormones, virostatic agents, experimental drugs, or other anticancer therapy; known hypersensitivity reaction to investigational compounds; known dihydropyrimidine dehydrogenase deficiency Notes: 54.7% were node-positive 64.7% were hormone receptor-positive 30% were HER2-positive 22.9% were triple-negative
Interventions	Neoadjuvant setting ARM 1 (EC-TX): (N = 479) epirubicin (90 mg/m² IV Day 1) plus cyclophosphamide (600 mg/m² IV Day 1) every 3 weeks for 4 cycles followed by docetaxel (75 mg/m² IV Day 1) plus capecitabine (900 mg/m² twice daily oral Days 1 to 14) every 3 weeks for 4 cycles ARM 2 (EC-T-X): epirubicin (90 mg/m² IV Day 1) plus cyclophosphamide (600 mg/m² IV Day 1) every 3 weeks for 4 cycles followed by docetaxel (75 mg/m² IV Day 1) every 3 weeks for 4 cycles followed by capecitabine (900 mg/m² twice daily oral Days 1 to 14) every 3 weeks for 4 cycles ARM 3 (EC-T): epirubicin (90 mg/m² IV Day 1) plus cyclophosphamide (600 mg/m² IV Day 1) every 3 weeks for 4 cycles followed by docetaxel (100 mg/m² IV Day 1) every 3 weeks for 4 cycles Notes: Lower dose of docetaxel was used in capecitabine-containing arms (75 mg/m² vs 100 mg/m²) EC-T-X regimen was longer than the other regimens (36 weeks vs 24 weeks) Ultrasound assessment of the tumour was performed in the final week of EC; if there was tumour progression at that time, patients discontinued treatment and were not randomised Other adjuvant therapy: trastuzumab was given to all patients with HER2-positive disease (8 mg/kg IV loading dose Day 1 cycle 1, then 6 mg/kg IV Day 1 every 3 weeks from cycle 2 onwards) G-CSF and ciprofloxacin were given if needed as secondary prophylaxis for febrile neutropenia
Outcomes	Primary: pathological complete response rate (assessed locally according to modified regression grading system: grade 5, no microscopic evidence of residual viable tumour cells (invasive or non-invasive) in breast and nodes; grade 4, no residual tumour in breast tissue but involved nodes; grade 3, only residual non-invasive tumour in breast tissue; grade 2, focal invasive tumour measuring ≤ 5 mm; grades 0 to 1 for all remaining scenarios. If new lesions were detected, response was graded as 0 to 1. Regression grades 4 and 5 were considered pCR. Reports were centrally reviewed at German Breast Group headquarters) Secondary: rate of breast conserving surgery (tumourectomy, segmentectomy, or quadrantectomy as the final surgical procedure); response rate at surgery according to mid-course response after 4 cycles EC and in patients with stage cT4a to d disease; frequency of use of sentinel node biopsy (SNB) before chemotherapy for selecting patients for neoadjuvant chemotherapy and at surgery to avoid axillary clearance; toxicity; compliance; disease-free survival; overall survival
Identification	Trial registration link: https://clinicaltrials.gov/ct2/show/NCT00288002 Funding considerations: The trial received funding support from Roche and Sanofi-Aventis. Funders had no access to the study database and were not involved in analysis and interpretation of results **Author's name:** Gunter von Minckwitz

GeparQuattro *(Continued)*

	Institution: Frankfurt University, German Breast Group **Email:** gunter.vonminckwitz@germanbreastgroup.de **Address:** German Breast Group, Forschungs GmbHMartin-Behaim-Strasse, 1263263 Neu-Isenburg, Germany
Notes	All randomised patients were included in intention-to-treat efficacy analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised randomisation by dynamic allocation with 1:1:1 ratio, with appropriate stratification factors
Allocation concealment (selection bias)	Low risk	Centralised randomisation with presumed allocation concealment but no explicit description of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) Overall survival	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Disease-free survival (DFS)	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Pathologic complete response (pCR) - neoadjuvant studies only	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Toxicities	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, high risk due to difference in toxicity profile
Incomplete outcome data (attrition bias) All outcomes	Low risk	All listed outcomes reported on. All patients accounted for in Intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Adequate reporting of pre-specified primary and secondary endpoints
Other bias	Low risk	No other sources of bias detected

ICE

Study characteristics

Methods	Accrual time: June 2004 to August 2008

ICE *(Continued)*

	Multi-centre: Germany (150 sites) Phase 3 open-label randomised controlled trial Median follow-up: 61.3 months Baseline comparability: balanced
Participants	N = 1358 females Age: median 71 years (range 64 to 88) Diagnosis: invasive breast cancer Inclusion criteria: age ≥ 65; pathological node-positive or tumour ≥ 2 cm in diameter or grade 2 or 3 or hormone receptor-negative; Charlson Index ≤ 2; no prior chemotherapy; adequate organ function Exclusion criteria: not described Notes: 48.1% were node-positive 81% were hormone receptor-positive 18.8% were HER2-positive 14.1% were triple-negative
Interventions	Adjuvant setting ARM 1 (IX): ibandronate (50 mg oral daily or 6 mg IV Q4W) for 2 years plus capecitabine (1000 mg/m^2 twice daily oral Days 1 to 14) every 3 weeks for 6 cycles ARM 2 (I): ibandronate (50 mg oral daily or 6 mg IV Q4W) for 2 years Other adjuvant therapies
Outcomes	Primary: event-free survival Secondary: overall survival; compliance; toxicity; bone-related events (fracture, surgery, new osteoporosis) in hormone-sensitive and -insensitive disease (with or without endocrine treatment); preference for route of administration of ibandronate (oral vs IV); geriatric assessments by Charlson score vs VES 13 score; biomarkers
Identification	Trial registration link: https://clinicaltrials.gov/ct2/show/NCT00196859 Funding: Roche, AstraZeneca. Funders had no access to the study database and were not involved in analysis and interpretation of results **Author's name:** Gunter von Minckwitz **Institution:** German Breast Group **Email:** toralf.reimer@med.uni-rostock.de **Address:** Department of Obstetrics and Gynecology, University of Rostock, Klinikum Suedstadt, Suedring 81, 18059 Rostock, Germany
Notes	Not all randomised patients were included in intention-to-treat analysis - only those who started treatment and provided documentation Hazard ratios were inverted from published data

ICE *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method unclear, as not yet published
Allocation concealment (selection bias)	Unclear risk	Method unclear, as not yet published
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) Overall survival	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Disease-free survival (DFS)	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Toxicities	High risk	Given unblinded study and marked difference in toxicities, high risk due to difference in toxicity profile
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited patients accounted for at each stage of analysis and included in ITT analysis. Note: not yet fully reported
Selective reporting (reporting bias)	Low risk	Reported outcomes were pre-specified and were presented completely
Other bias	Unclear risk	Not yet fully reported, thus consensus was that this is unclear, but no overt other sources of bias identified

IMELDA

Study characteristics	
Methods	Accrual time: 16 July 2009 to 7 March 2011 Multi-centre: Brazil, China, Egypt, France, Hong Kong, India, Italy, Poland, Spain, Turkey (54 centres) Phase 3 open-label randomised controlled trial Median follow-up: 30.4 months Baseline comparability: capecitabine group had younger median age (49 vs 54 years) and had fewer widespread metastases (47.3% vs 57.4%, with metastasis to ≥ 3 organs)
Participants	N = 185 Age: median 49 years (range 24 to 80) in the capecitabine arm; 54 years (range 24 to 77) in the comparator arm

IMELDA *(Continued)*

	Diagnosis: metastatic HER2-negative breast cancer Inclusion criteria: HER2-negative breast cancer; measurable metastatic disease; ECOG < 2; no prior chemotherapy for metastatic breast cancer; adequate bone marrow, renal, and liver function; no progressive disease after 3 to 6 cycles of bevacizumab and docetaxel Exclusion criteria: presence of brain metastases; major surgical procedure < 28 days before start of study treatment; uncontrolled hypertension; history or evidence of coagulopathy with risk of bleeding; history of abdominal fistula, grade 4 bowel obstruction, gastrointestinal perforation, or intra-abdominal abscess < 6 months before first study dose; spinal cord compression; pre-existing peripheral neuropathy grade 3 or worse; known dihydropyrimidine dehydrogenase deficiency Notes: 75.1% were hormone receptor-positive 0% were HER2-positive 24.9% were triple-negative
Interventions	First-line metastatic setting All patients were initially treated with Bev/T: bevacizumab (15 mg/kg IV Day 1) plus docetaxel (75 to 100 mg/m² IV Day 1) every 3 weeks for 6 cycles If tumour response demonstrated stable disease, partial response, or complete response after 6 cycles, patient was randomised (If there was tumour response by 3 cycles and toxicity required docetaxel interruption, patient could proceed to randomisation and second part) ARM 1 (Bev/X): (N = 91) bevacizumab (15 mg/kg IV Day 1) plus capecitabine (1000 mg/m² twice daily oral Days 1 to 14) every 3 weeks until disease progression/toxicity/withdrawal ARM 2 (Bev): (N = 94) bevacizumab (15 mg/kg IV Day 1) every 3 weeks until disease progression/toxicity/withdrawal No co-interventions reported
Outcomes	Primary: investigator-assessed progression-free survival (time from randomisation until disease progression or death) Secondary: In initial (bevacizumab and docetaxel) treatment phase: objective response rate (based on best overall response) or clinical benefit (documented complete or partial response, or stable disease); safety. In maintenance phase: overall survival (time from randomisation to death); safety; proportions of patients achieving objective response or clinical benefit (complete or partial response, stable disease); time to progression; quality of life
Identification	Trial registration link: https://clinicaltrials.gov/ct2/show/NCT00929240 Funding considerations: F. Hoffmann-La Roche. The study was designed by the trial steering committee and representatives from Roche. Data were collected and analysed by a clinical research organisation, Chiltern International (Slough, UK) **Author's name:** J Gligorov **Institution:** APHP Tenon, IUC-UPMC, Paris, FRANCE **Email:** joseph.gligorov@tnn.aphp.fr **Address:** APHP Tenon, IUC-UPMC, Paris, FRANCE

IMELDA *(Continued)*

Notes	All randomised patients were included in intention-to-treat analysis for efficacy outcomes; per-protocol population (all patients who received ≥ 1 dose of maintenance treatment) was analysed for safety

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised with an interactive voice-response system by block (size 4) randomisation (1:1). No explicit comment on sequence generation
Allocation concealment (selection bias)	Low risk	Presumed randomisation was centralised given randomisation process described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) Overall survival	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Progression-free survival (PFS)	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, assessed to be at high risk of bias because outcome can be subjective
Blinding of outcome assessment (detection bias) Overall response rate (ORR)	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, assessed to be at high risk of bias because outcome can be subjective
Blinding of outcome assessment (detection bias) Clinical benefit rate	High risk	Clinical benefit reported but only as a number, not as a rate. No explicit comment as to blinding of outcome assessment. Given unblinded study, assessed to be at high risk because outcome can be subjective
Blinding of outcome assessment (detection bias) Toxicities	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, high risk due to difference in toxicity profile
Blinding of outcome assessment (detection bias) Quality of life (QoL) - metastatic studies only	Unclear risk	Given the heterogeneity of treatment arms; both have clear pros and cons for quality of life. As this was an unblinded study and this outcome is subjective, this study was deemed to be at unclear risk
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited patients accounted for at each stage of analysis and included in ITT analysis
Selective reporting (reporting bias)	High risk	Study terminated early; sample size not reached. Unable to obtain mature data on survival, and no data on subsequent treatments recorded systematically. Quality of life data not reported
Other bias	Low risk	No other sources of bias detected

Lee 2008

Study characteristics	
Methods	Accrual time: June 2002 to April 2005 Single-centre: Korea Phase 3 open-label randomised controlled trial Median follow-up: 52.3 months Baseline comparability: could not be assessed
Participants	N = 209 Age: median 44 years (21 to 67) Diagnosis: stage II or III invasive breast cancer Inclusion criteria: age ≥ 18; ECOG ≤ 1; biopsy-proven newly diagnosed stage II/III breast cancer with axillary lymph node involvement; adequate bone marrow, hepatic, renal, cardiac, and mental function Exclusion criteria: prior surgery, hormonal treatment, chemotherapy, radiotherapy, or history of cancer except for in situ uterine cervical cancer or non-melanocytic skin cancer; received dose-reduced chemotherapy Notes: 100% were node-positive 61.8% were hormone receptor-positive 80.4% were HER2-positive (2+ or 3+ on IHC) Triple-negative rate was not reported
Interventions	Neoadjuvant setting ARM 1 (neoadjuvant TX/adjuvant AC): (N = 103) docetaxel (36 mg/m² IV Day 1) plus capecitabine (1000 mg/m² twice daily oral Days 1 to 14) every 3 weeks for 4 cycles followed by surgery, then followed by doxorubicin (60 mg/m² IV Day 1) plus cyclophosphamide (600 mg/m² IV Day 1) every 3 weeks for 4 cycles ARM 2 (neoadjuvant AC/adjuvant TX): (N = 101) doxorubicin (60 mg/m² IV Day 1) plus cyclophosphamide (600 mg/m² IV Day 1) every 3 weeks for 4 cycles followed by surgery, then followed by docetaxel (36 mg/m² IV Day 1) plus capecitabine (1000 mg/m² twice daily oral Days 1 to 14) every 3 weeks for 4 cycles Growth factor support not reported Other adjuvant therapies: all patients completing adjuvant chemotherapy received radiotherapy concurrent with tamoxifen or anastrozole when hormone receptor-positive Anti-HER2 therapy was not reported
Outcomes	Primary: pathological complete response Secondary: clinical response rate; toxicity; disease-free survival; overall survival
Identification	Trial registration link: https://clinicaltrials.gov/ct2/show/NCT00352378 Funding considerations: supported in part by NCC Grant 0210150 and Korean Health R&D Project Grant by Ministry of Heath and Welfare, Republic of Korea (0412-CR01-0704-0001). Sanofi-Aventis and Roche Korea provided study drugs, Taxotere and Xeloda, respectively

Lee 2008 *(Continued)*

Author's name: J. Ro

Institution: Research Institute and Hospital, National Cancer Center

Email: jungsro@ncc.re.kr

Address: 809 Madu-1-dong, Ilsan-go, Goyang-si, Gyeonggi-do, 410-769, Republic of Korea

Notes	Not all randomised patients were included in intention-to-treat analysis – only those who underwent surgery were analysed OS and DFS not reported by HR status; no data reported on mean number of months of survival, only % survival at 1, 2, 3, 4 years; such hazard ratio calculated by Tierney method

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation of block size 4 with appropriate stratification factors
Allocation concealment (selection bias)	Low risk	Centralised randomisation with presumed allocation concealment but no explicit comment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) Overall survival	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Disease-free survival (DFS)	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Pathologic complete response (pCR) - neoadjuvant studies only	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Toxicities	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, high risk due to difference in toxicity profile
Incomplete outcome data (attrition bias) All outcomes	High risk	All recruited patients accounted for at each stage of analysis. Not all patients included in ITT analysis
Selective reporting (reporting bias)	Low risk	Focus on pCR with no subgroup analyses of secondary outcomes, but otherwise satisfactory
Other bias	High risk	Receipt of post-surgery treatments unclear, with patients crossing over to receive alternate treatment post surgery. Dose intensity of adjuvant treatments not reported. Additionally, receipt of endocrine therapy or trastuzumab not reported. These weaknesses would influence DFS and OS but would not affect pCR - the primary endpoint of the study

METRIC

Study characteristics	
Methods	Accrual time: February 2014 to August 2017 Multi-centre: 120 institutions Phase 2b open-label randomised controlled trial Median follow-up: not reported Baseline comparability: well balanced
Participants	N = 327 women Age: median 55 years Diagnosis: metastatic triple-negative breast cancer with gpNMB over-expression Inclusion criteria: gpNMB over-expression (> 25% tumour cells positive by central immunohistochemistry of archival tissue); oestrogen and progesterone receptor expression < 10% and HER2-negative; ECOG 0 to 1; prior taxane; prior anthracycline exposure (if indicated); < 2 chemotherapy regimens for advanced BC; no progression < 3 months from neo/adjuvant chemotherapy Exclusion criteria: not listed in abstract Note: Entire cohort triple-negative
Interventions	Metastatic ARM 1 (glembatumumb vedotin): N = 218 Glembatumumab vedotin 1.88 mg/kg given intravenously on Day 1 for a 21-day cycle, until progression or intolerance ARM 2 (capecitabine): N = 109 Capecitabine 1250 mg/m^2 given orally twice a day for 14 days on a 21-day cycle, until progression or intolerance
Outcomes	Primary: progression-free survival per independent, blinded central review using RECIST 1.1 Secondary: overall survival; objective response rate; duration of response; safety; pharmacokinetics
Identification	Trial registration link: https://clinicaltrials.gov/ct2/show/NCT01997333 Funding considerations: Celldex Therapeutics, Inc. **Author's name:** P. Schmid **Institution:** Centre for Experimental Cancer Medicine, Barts Cancer Institute-Queen Mary University of London, London, UK
Notes	All randomised patients were included in intention-to-treat analysis Outcomes were reported from abstract and poster Hazard ratios were inverted from published data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised 2:1; no specific details as to randomisation method
Allocation concealment (selection bias)	Unclear risk	No explicit description of allocation concealment
Blinding of participants and personnel (performance bias)	High risk	Open-label study

METRIC *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) Overall survival	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Progression-free survival (PFS)	Low risk	Independent blinded central radiological review
Blinding of outcome assessment (detection bias) Overall response rate (ORR)	Low risk	Independent blinded central radiological review
Blinding of outcome assessment (detection bias) Toxicities	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, high risk due to difference in toxicity profile
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Discussion of number screened, randomised. No reasons given for dropout. Outcomes assessed by ITT population
Selective reporting (reporting bias)	Low risk	Adequate reporting of pre-specified primary and secondary endpoints
Other bias	Unclear risk	Outcomes available only by poster and abstract. No obvious other sources of bias, but this can be confirmed only by full publication

NSABP-40

Study characteristics	
Methods	Accrual time: 5 January 2007 to 30 June 2010 Multi-centre: United States, Canada, Puerto Rico (442 sites) Phase 3 open-label randomised controlled trial Median follow-up: 4.7 years Baseline comparability: balanced
Participants	N = 1206 females Age: 52.2% ≤ 49 years; 31.6% 50 to 59 years; 16.2% ≥ 60 years Diagnosis: invasive HER2-negative breast cancer Inclusion criteria: age ≥ 18 years; operable HER2-non-amplified invasive breast adenocarcinoma; palpable primary tumour ≥ 2.0 cm in diameter in the breast, as assessed by physical examination; tumour stage T1c to T3, nodal stage N0 to N2a, and metastasis stage M0; ECOG 0 to 1; normal LVEF; adequate hepatic and renal function; no previous treatment for breast cancer, with the only exception being hormonal therapy Exclusion criteria: HER2-positive disease; T1a and b (tumour < 2 cm diameter); T4; N2b, N3; history of other malignancies, unless considered disease-free for 5 years or longer; cardiac disease; history of transient ischaemic attack or cerebrovascular accident; other arterial thrombotic event within 12

NSABP-40 *(Continued)*

	months; symptomatic peripheral vascular disease; non-traumatic bleeding within 6 months; non-healing wounds or fractures; gastroduodenal ulcers; recent invasive procedures; known bleeding diathesis or coagulopathy; neuropathy ≥ grade 2; any condition that would preclude treatment with regimens in the protocol or corticosteroids; pregnancy or lactation; life expectancy < 10 years excluding diagnosis of breast cancer Notes: 47.3% were node-positive 60.4% were hormone receptor-positive 0% were HER2-positive 41.3% were triple-negative
Interventions	Neoadjuvant setting ARM 1 (TX-AC): (N = 204) docetaxel (75 mg/m² IV Day 1) plus capecitabine (825 mg/m² twice daily oral Days 1 to 14) every 3 weeks for 4 cycles followed by doxorubicin (60 mg/m² IV Day 1) plus cyclophosphamide (600 mg/m² IV Day 1) every 3 weeks for 4 cycles ARM 2 (TX-AC + bev): (N = 201) docetaxel (75 mg/m² IV Day 1) plus bevacizumab (15 mg/kg IV Day 1) plus capecitabine (825 mg/m² twice daily oral Days 1 to 14) every 3 weeks for 4 cycles followed by doxorubicin (60 mg/m² IV Day 1) plus cyclophosphamide (600 mg/m² IV Day 1) plus bevacizumab (15 mg/kg IV Day 1) every 3 weeks for 2 cycles, then doxorubicin and cyclophosphamide without bevacizumab for 2 cycles. This was followed by surgery, then adjuvant bevacizumab (15 mg/kg IV Day 1) every 3 weeks for 10 cycles ARM 3 (T-AC): (N = 201) docetaxel (100 mg/m² IV Day 1) every 3 weeks for 4 cycles followed by doxorubicin (60 mg/m² IV Day 1) plus cyclophosphamide (600 mg/m² IV Day 1) every 3 weeks for 4 cycles ARM 4 (T-AC + bev): (N = 199) docetaxel (100 mg/m² IV Day 1) plus bevacizumab (15 mg/kg IV Day 1) every 3 weeks for 4 cycles followed by doxorubicin (60 mg/m² IV Day 1) plus cyclophosphamide (600 mg/m² IV Day 1) plus bevacizumab (15 mg/kg IV Day 1) every 3 weeks for 2 cycles followed by doxorubicin plus cyclophosphamide without bevacizumab for 2 cycles. This was followed by surgery, then adjuvant bevacizumab (15 mg/kg IV Day 1) every 3 weeks for 10 cycles ARM 5 (TG-AC): (N = 197) docetaxel (75 mg/m² IV Day 1) plus gemcitabine (1000 mg/m² IV Day 1 and Day 8) every 3 weeks for 4 cycles followed by doxorubicin (60 mg/m² IV Day 1) plus cyclophosphamide (600 mg/m² IV Day 1) every 3 weeks for 4 cycles ARM 6 (TG-AC + bev): (N = 204) docetaxel (75 mg/m² IV Day 1) plus gemcitabine (1000 mg/m² IV Day 1 and Day 8) plus bevacizumab (15 mg/kg IV Day 1) every 3 weeks for 4 cycles followed by doxorubicin (60 mg/m² IV Day 1) plus cyclophosphamide (600 mg/m² IV Day 1) plus bevacizumab (15 mg/kg IV Day 1) every 3 weeks for 2 cycles followed by doxorubicin plus cyclophosphamide without bevacizumab for 2 cycles. This was followed by surgery, then adjuvant bevacizumab (15 mg/kg IV Day 1) every 3 weeks for 10 cycles Growth factor support not reported Note: Lower dose of docetaxel was used in combination with capecitabine or gemcitabine (75 mg/m² vs 100 mg/m²)
Outcomes	Primary: pathological complete response rate (absence of histological evidence of invasive tumour cells in surgical breast specimen) Secondary: pathological complete response rate in breast and nodes (absence of histological evidence of invasive tumour cells in surgical breast specimen, axillary nodes, and non-axillary sentinel nodes identified after neoadjuvant chemotherapy); clinical complete response rate after docetaxel-based portion of neoadjuvant chemotherapy completed; clinical complete response rate after all neoadjuvant chemotherapy completed; cardiac event rate (NYHA Class III or IV heart failure); toxicity (including

NSABP-40 *(Continued)*

	cardiac events other than congestive cardiac failure); surgical complication rate; disease-free survival (local recurrence following mastectomy, local recurrence in the ipsilateral breast following lumpectomy, regional recurrence, distant recurrence, contralateral breast cancer, second primary cancer (other than squamous or basal cell carcinoma of the skin, melanoma in situ, carcinoma in situ of the cervix, colon carcinoma in situ, or lobular carcinoma in situ of the breast), death from any cause before recurrence or second primary cancer)
Identification	Trial registration link: https://clinicaltrials.gov/ct2/show/NCT004084081 Funding considerations: supported in part by F. Hoffmann–La Roche, Genentech USA, and Eli Lilly Funders had no role in study design, data collection, data analysis or data interpretation, writing of the report, or decision to submit the paper for publication. The NSABP restricts sponsor access to outcomes data until submission of an abstract **Author's name:** Harry D Bear **Institution:** Massey Cancer Centre, Virginia Commonwealth University, Richmond **Email:** hdbear@vcu.edu **Address:** Box 980011, Division of Surgical OncologyVirginia Commonwealth University, Richmond, VA 23298-0011, USA
Notes	Primary analysis was performed in intention-to-treat analysis of all randomised patients for whom outcomes were ascertained. Secondary analyses were performed on eligible patients only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified randomisation is reasonable in this situation
Allocation concealment (selection bias)	Low risk	Chemotherapy commenced as soon as possible after randomisation, as discussed in trial protocol
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) Overall survival	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Disease-free survival (DFS)	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Pathologic complete response (pCR) - neoadjuvant studies only	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Toxicities	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, high risk due to difference in toxicity profile

NSABP-40 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Adequate reporting of pre-specified primary and secondary endpoints; all randomised patients included in ITT analysis
Selective reporting (reporting bias)	Low risk	Adequate reporting of pre-specified primary and secondary endpoints
Other bias	Low risk	No other sources of bias detected

Pallis 2012

Study characteristics	
Methods	Accrual time: April 2002 to December 2008 Multi-centre: Greece Phase 3 open-label randomised controlled trial Median follow-up: 34.3 months for capecitabine arm; 32.8 months for comparator arm Baseline comparability: balanced
Participants	N = 158 females Age: median 60 years (range 32 to 82) Diagnosis: metastatic breast cancer Inclusion criteria: histologically or cytologically confirmed metastatic breast cancer; adjuvant or metastatic treatment with anthracyclines and taxanes; age ≥ 18 years; ≥ 1 measurable lesion according to RECIST criteria; ECOG 0 to 2; life expectancy > 3 months; adequate organ function; CNS metastases allowed if irradiated and stable Exclusion criteria: no previous anthracycline chemotherapy; no previous taxane chemotherapy; active infection; history of significant cardiac disease; malnutrition (loss of ≥ 20% of original weight) Notes: 81.5% in capecitabine arm and 69% in comparator arm were hormone receptor-positive 13.5% were HER2-positive Triple-negative rate was not reported
Interventions	Metastatic setting (any line; must have had anthracycline and taxane therapy in neoadjuvant, adjuvant, or metastatic setting) ARM 1 (X): (N = 74) capecitabine (1250 mg/m^2 twice daily oral Days 1 to 14) every 3 weeks for 6 cycles ARM 2 (VG): (N = 74) vinorelbine (25 mg/m^2 IV Day 1 and Day 8) plus gemcitabine (1000 mg/m^2 IV Day 1 and Day 8) every 4 weeks for 6 cycles Notes: Two responding patients continued therapy for > 6 cycles Growth factor support at physician discretion; use not reported
Outcomes	Primary: progression-free survival

Pallis 2012 *(Continued)*

	Secondary: objective response rate; safety; overall survival
Identification	Trial registration link: https://clinicaltrials.gov/ct2/show/NCT00431106 Funding considerations: unstated - no conflicts declared, so possibly investigator initiated **Author's name:** D. Mavroudis **Institution:** Department of Medical Oncology, University General Hospital of Heraklion **Email:** mavrudis@med.uoc.gr **Address:** University General Hospital of Heraklion, 711 10 Heraklion, Crete, Greece
Notes	Hazard ratios were inverted from published data All randomised patients were not included in intention-to-treat analysis. Only patients who received treatment were included in outcome analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	No description of method of randomisation in text, but large multi-centre trial; presumed to use reasonable randomisation methods
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) Overall survival	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Progression-free survival (PFS)	Low risk	Central radiological review of all imaging to confirm responses. Therefore we judge this outcome to be at low risk of bias
Blinding of outcome assessment (detection bias) Overall response rate (ORR)	Low risk	ORR was assessed by central CT review of all scans to confirm responses. Therefore we judged this outcome to be at low risk of bias
Blinding of outcome assessment (detection bias) Toxicities	High risk	Given unblinded study, high risk due to difference in toxicity profile
Incomplete outcome data (attrition bias) All outcomes	High risk	10 randomised patients who withdrew consent or died pre-therapy were not included in ITT analysis
Selective reporting (reporting bias)	Low risk	Adequate reporting of pre-specified primary and secondary endpoints
Other bias	Low risk	No other sources of bias detected

Seidman 2011

Study characteristics	
Methods	Accrual time: February 2002 to December 2008 Multi-centre:Argentina, Australia, Brazil, Mexico, South Korea, Taiwan, United States (90 centres) Phase 3 open-label randomised controlled trial Median follow-up: 20.6 months for capecitabine arm; 19.6 months for comparator arm Baseline comparability: balanced
Participants	N = 489 females Age: median 54 years (range 27 to 82) in capecitabine arm; 57 years (27 to 81) in comparator arm Diagnosis: locally advanced or metastatic breast cancer Inclusion criteria: age ≥ 18 years with histologically or cytologically confirmed locally advanced or metastatic disease; life expectancy ≥ 12 weeks; ECOG 0 to 1; adequate renal, hepatic, and bone marrow function; may have completed neoadjuvant or adjuvant taxane therapy ≥ 6 months before enrolment; prior anthracycline, hormone, or immunotherapy and no more than 1 prior line of chemotherapy for metastatic breast cancer; radiation therapy to < 25% of bone marrow allowed ≥ 4 weeks before enrolment, provided patients had recovered from all side effects Exclusion criteria: prior taxane therapy for metastatic breast cancer; prior therapy with gemcitabine or capecitabine; ongoing concomitant trastuzumab therapy; brain metastasis Notes: 56.6% were ER-positive 45.7% were PR-positive HER2 status was not reported 88.2% had not had prior chemotherapy for metastatic disease
Interventions	First- or second-line metastatic setting ARM 1 (CD): (N = 236) docetaxel (75 mg/m² IV Day 1) plus capecitabine (1000 mg/m² orally twice daily Days 1 to 14) every 3 weeks ARM 2 (GD): (N = 239) docetaxel (75 mg/m² IV Day 1) plus gemcitabine (1000 mg/m² IV Day 1 and Day 8) every 3 weeks At time of disease progression, patients were crossed over to receive single-agent gemcitabine or capecitabine (as per above doses) Use of G-CSF, erythropoietin, and antiemetics was allowed but was not reported
Outcomes	Primary: time to progression Secondary: overall response rate; overall survival (number of months between date of randomisation and date of death from any cause, censored at date of last contact for patients who were still alive); adverse events
Identification	Trial registration link: https://clinicaltrials.gov/ct2/showNCT00191152 Funding considerations: Eli Lilly **Author's name:** A.D. Seidman

Seidman 2011 *(Continued)*

	Institution: Memorial Sloan Kettering Cancer Center **Email:** seidmana@mskcc.org **Address:** Department of Medicine, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10021 USA
Notes	All randomised participants were included in intention-to-treat analysis Hazard ratios were inverted from published data No outcome data were reported by ER or hormone receptor status. Pooled analysis (with Chan 2009) was published in Seidman 2014. All references to Seidman 2014 in data analysis are labelled under Seidman 2011 but are referenced in notes of the relevant table, as Seidman 2014

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	No description of method of randomisation in text, but large multi-centre trial; presumed to use reasonable randomisation methods
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) Overall survival	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Progression-free survival (PFS)	High risk	Reported as time to progression rather than as PFS. No explicit comment as to blinding of outcome assessment. Given unblinded study, assessed to be at high risk of bias because outcome can be subjective
Blinding of outcome assessment (detection bias) Overall response rate (ORR)	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, assessed to be at high risk of bias because outcome can be subjective
Blinding of outcome assessment (detection bias) Toxicities	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, high risk due to difference in toxicity profile
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited patients accounted for at each stage of analysis and included in ITT analysis
Selective reporting (reporting bias)	High risk	Intended analyses well described and delivered, but only 398 of 463 patients assessed for response by RECIST. Of patients who discontinued, only 324 assessed for TtP (time to progression) median; however all included in Kaplan-Meier curves - thus incomplete reporting
Other bias	Unclear risk	Cross-over allowed, potentially could dilute survival outcomes

Seidman 2011 *(Continued)*

	Pooled analysis performed with Chan 2009

SO140999

Study characteristics	
Methods	Accrual time: not reported Multi-centre: Argentina, Australia, Brazil, Canada, France, Germany, Israel, Italy, Mexico, New Zealand, Norway, Russia, Spain, Taiwan, United Kingdom, United States of America Phase 3 open-label randomised controlled trial Median follow-up: not reported Baseline comparability: balanced
Participants	N = 511 females Age: mean 52 years (range 26 to 79) in capecitabine arm; 51 years (range 25 to 75) in comparator arm Diagnosis: unresectable locally advanced or metastatic breast cancer Inclusion criteria: age ≥ 18 years; histologically or cytologically confirmed breast cancer with unresectable locally advanced and/or metastatic disease; ≥ 1 bi-dimensionally measurable lesion that had not been irradiated, with a minimum size in ≥ 1 diameter ≥ 20 mm for liver lesions and ≥ 10 mm for lung, skin, and lymph node metastases; recurrence after anthracycline treatment defined as (1) progression while receiving anthracycline-based chemotherapy without experiencing any transient improvement; (2) no response after administration of ≥ 4 cycles of anthracycline-based chemotherapy; (3) relapsing within 2 years of completing (neo)adjuvant anthracycline-based chemotherapy; or (4) a brief objective response to anthracycline-based chemotherapy with subsequent progression while receiving the same therapy or within 12 months after the last dose; Karnofsky performance score ≥ 70% and life expectancy ≥ 3 months Exclusion criteria: prior docetaxel-containing regimen; ≥ 3 chemotherapy regimens for advanced/metastatic disease; radiotherapy to the axial skeleton within 4 weeks of treatment start; hormonal therapy within 10 days of treatment start; chemotherapy within 4 weeks of treatment start; clinically significant cardiac disease; evidence of CNS metastases; known hypersensitivity to 5-FU; prior unanticipated, severe reactions to drugs formulated with polysorbate 80 (e.g. taxanes) or to fluoropyrimidines Notes: 50.8% were hormone receptor-positive (of patients whose ER and PR status was available) 29.4% had missing ER status and a further 10.8% had ER status available but were missing PR status HER2 status was not reported Triple-negative rate was not reported Number of previous chemotherapy lines was not reported
Interventions	First-, second- or third-line metastatic setting ARM 1 (CD): (N = 251) docetaxel (75 mg/m² IV Day 1) plus capecitabine (1250 mg/m² twice daily oral Days 1 to 14) every 3 weeks until disease progression or unacceptable toxicity ARM 2 (D): (N = 255) docetaxel (100 mg/m² IV Day 1) every 3 weeks until disease progression or unacceptable toxicity

SO140999 *(Continued)*

	No co-interventions reported Note: lower dose of docetaxel was used in combination with capecitabine (75 mg/m² vs 100 mg/m²)
Outcomes	Primary: time to progression (time from randomisation to progressive disease or death in patients with no evidence of progressive disease) Secondary: overall response rate, overall survival Note: later exploratory analyses by ER status assessed time to progression as the primary objective, along with overall response rate, overall survival, and clinical benefit rate
Identification	Trial registration link: not available Funding considerations: Hoffman-La Roche and Genentech. The Sponsor funded the original study and data analysis. However, critical aspects of this exploratory analysis such as generation of research hypotheses, key data elements for inclusion in the analyses, and result interpretations were led by non-Genentech authors. Statistical programming support came from Bokai Xia, and support for third-party writing assistance was provided by Hoffmann-La Roche Inc. **Author's name:** S. Glück **Institution:** Sylvester Comprehensive Cancer Center **Email:** SGluck@med.miami.edu **Address:** Department of Medicine, Division of Hematology/Oncology, University of Miami, Leonard M Miller School of Medicine, Sylvester Comprehensive Cancer Center, 1475 NW 12th Avenue, Miami, FL 33136, USA
Notes	All randomised patients were included in intention-to-treat analysis Randomisation was not stratified by ER status in original trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised by country using a block size of 4 via computer-assisted, touch-tone, central randomisation service in 2 locations - USA and Europe. Previous treatment with paclitaxel was the only variable used for stratification
Allocation concealment (selection bias)	Low risk	Centralised randomisation with presumed allocation concealment but no explicit comment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded study
Blinding of outcome assessment (detection bias) Overall survival	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Progression-free survival (PFS)	High risk	Progression-free survival not collected, reported instead as time to progression. No explicit comment as to blinding of outcome assessment. High risk of bias because outcome may be subjective
Blinding of outcome assessment (detection bias)	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, assessed to be at high risk of bias because outcome can be subjective

SO140999 *(Continued)*

Overall response rate (ORR)		
Blinding of outcome assessment (detection bias) Clinical benefit rate	High risk	Considered to be at high risk of bias as outcome is subjective
Blinding of outcome assessment (detection bias) Toxicities	High risk	Given unblinded study, high risk due to the difference in toxicity profile
Blinding of outcome assessment (detection bias) Quality of life (QoL) - metastatic studies only	Unclear risk	Given the heterogeneity of treatment arms; both have clear pros and cons for quality of life. As this was an unblinded study and this outcome is subjective, this study was deemed to be at unclear risk
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited patients accounted for at each stage of analysis and included in ITT analysis
Selective reporting (reporting bias)	High risk	Adequate reporting of all specified primary and secondary outcomes. Incomplete reporting of outcomes by hormone receptor status
Other bias	Low risk	No other sources of bias detected

Study 301

Study characteristics	
Methods	Accrual time: September 2006 to September 2009 Multi-centre: USA, Canada, Mexico, Argentina, Brazil, Russia, Serbia, Czech Republic, Germany, Belgium, United Kingdom, Spain, Italy, Greece, Hungary, Romania, Croatia, Israel, Bulgaria, Lithuania, Poland, Ukraine, Taiwan, Singapore, Australia (169 sites) Phase 3 open-label randomised controlled trial Median follow-up: not reported Baseline comparability: balanced
Participants	N = 1102 females Age: median 53 years (range 26 to 80) in capecitabine arm; 54 (24 to 80) in comparator arm Diagnosis: locally advanced unresectable or metastatic breast cancer Inclusion criteria: female; age ≥ 18 years; histologically or cytologically confirmed breast cancer; up to 3 prior chemotherapy regimens and up to 2 prior chemotherapy regimens for advanced and/or metastatic disease; prior therapy with an anthracycline and a taxane Exclusion criteria: > 3 prior chemotherapy regimens for breast cancer, including adjuvant therapies; > 2 prior chemotherapy regimens for advanced disease (other therapies are allowed, e.g. hormonal treatment) Notes: 48.7% were oestrogen receptor-positive, and 41.8% were progesterone receptor-positive. ER or PR status was missing for 10.5% and 11.9%, respectively

Study 301 *(Continued)*

	15.3% were HER2-positive. HER2 status was missing for 16.2% 25.8% were triple-negative 20% had no prior chemotherapy, and 52% had 1 line of chemotherapy previously
Interventions	First-, second-, or third-line metastatic setting ARM 1 (X): capecitabine (1250 mg/m² twice daily Days 1 to 14) every 3 weeks ARM 2 (E): eribulin mesylate (1.4 mg/m² [= eribulin 1.23 mg/m²] IV Day 1 and Day 8) every 3 weeks G-CSF was received by 3.6% in the capecitabine arm and by 14.6% in the eribulin arm
Outcomes	Primary: overall survival (time from date of random assignment until date of death from any cause or last date known alive/data cutoff (censored)); progression-free survival (time from date of random assignment to date of recorded disease progression or death from any cause) Secondary: quality of life (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (version 3.0) and breast module Quality of Life Questionnaire BR23 (version 1.0)); objective response rate (RECIST 1.0, censored at last tumour assessment before subsequent anticancer therapy or before ≥ 2 missed scheduled tumour assessments, and confirmed by a second assessment ≥ 4 weeks after first observation of response; independent radiology review); duration of response (time from first documented complete or partial response until disease progression, death from any cause, or censoring at date of last tumour assessment); 1-, 2- and 3-year survival; tumour-related symptom assessment; safety; population pharmacokinetic/pharmacodynamic relationships (eribulin arm only)
Identification	Trial registration link: https://clinicaltrials.gov/ct2/show/NCT00337103 Funding considerations: Eisai Pharmaceutical Company. An independent data monitoring committee reviewed safety and efficacy data from interim analyses. The sponsor (Eisai, Woodcliff Lake, NJ) collected and analysed all data, with the exception of QoL analyses, which were analysed by Clinical Outcomes Solutions (Evergreen, CO) **Author's name:** Peter Kaufman **Institution:** Norris Cotton Cancer Centre **Email:** peter.a.kaufman@hitchcock.org **Address:** Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Lebanon, NH 03756
Notes	Hazard ratios were inverted from published data All randomised patients were included in intention-to-treat analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	No description of method of randomisation in text, but large multi-centre trial; presumed to use reasonable randomisation methods
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study

Study 301 *(Continued)*

Blinding of outcome assessment (detection bias) Overall survival	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Progression-free survival (PFS)	Low risk	Outcome was assessed through independent radiology review to confirm tumour response. Therefore this outcome was assessed to be at low risk of bias
Blinding of outcome assessment (detection bias) Overall response rate (ORR)	Low risk	ORR was assessed through independent radiology review to confirm tumour response. Therefore this outcome was assessed to be at low risk of bias
Blinding of outcome assessment (detection bias) Clinical benefit rate	Low risk	Clinical benefit rate defined in this study as CR, PR, or SD for ≥ 6 months. Outcome was assessed through independent radiology review to confirm tumour response. Therefore this outcome was assessed to be at low risk of bias
Blinding of outcome assessment (detection bias) Toxicities	High risk	Given unblinded study, high risk due to difference in toxicity profile
Blinding of outcome assessment (detection bias) Quality of life (QoL) - metastatic studies only	Unclear risk	Given the heterogeneity of treatment arms; both have clear pros and cons for quality of life. As this was an unblinded study and this outcome is subjective, this outcome was deemed to be at unclear risk
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited patients accounted for at each stage of analysis and included in ITT analysis
Selective reporting (reporting bias)	Low risk	Complete reporting of listed primary and secondary endpoints
Other bias	Unclear risk	Multiple papers, included pooled analyses, with unplanned post-hoc subgroup analyses of uncertain significance to bias

TABEA

Study characteristics	
Methods	Accrual time: September 2009 to October 2012 Multi-centre: Germany (57 sites) Phase 3 open-label randomised controlled trial Median follow-up: 26.1 months Baseline characteristics: balanced
Participants	N = 234 females Age: median 57 years (range 31 to 80) Diagnosis: locally advanced unresectable or metastatic HER2-negative breast cancer

TABEA *(Continued)*

	Inclusion criteria: histologically confirmed HER2-negative, locally advanced, or metastatic breast cancer not suitable for surgery, radiotherapy, or endocrine therapy alone; ≥ 6 months since (neo)adjuvant taxanes or capecitabine; cumulative previous dose < 360 mg/m² doxorubicin or 720 mg/m² epirubicin; adjuvant or palliative endocrine therapy or bisphosphonates allowed; measurable disease by RECIST; fully recovered from previous radiotherapy; ≥ 1 measurable lesion completely outside the radiation field or pathological proof of progressive disease; ECOG 0 to 2; adequate renal, cardiac, hepatic, and haematological function Exclusion criteria: prior chemotherapy for metastatic disease; brain metastases, unless adequately controlled by surgery and/or radiotherapy with complete resolution of symptoms and discontinuation of all steroids; prior malignancy in past 5 years; major surgery within last 28 days or anticipation of the need for major surgery during study treatment Notes: 77.5% were hormone receptor-positive 0% were HER2-positive 22.5% were triple-negative
Interventions	First-line metastatic setting ARM 1 (TBX): (N = 111) paclitaxel (80 mg/m² IV Days 1, 8, and 15) or docetaxel (75 mg/m² IV Day 1) (physician's choice) plus bevacizumab (15 mg/kg IV Day 1) plus capecitabine (900 mg/m² oral twice daily Days 1 to 14) every 3 weeks until disease progression or unacceptable toxicity ARM 2 (TB): (N = 116) paclitaxel (80 mg/m² IV Days 1, 8, and 15) or docetaxel (75 mg/m² IV Day 1) (physician's choice) plus bevacizumab (15 mg/kg IV Day 1) every 3 weeks until disease progression or unacceptable toxicity G-CSF was recommended according to protocols. Proportion in each arm that received growth factor support was not reported
Outcomes	Primary: progression-free survival Secondary: response rate; response duration; clinical benefit rate (complete response, partial response, or stable disease ≥ 24 weeks); 3-year overall survival; progression-free survival at age ≥ 65 years; toxicity; compliance
Identification	Trial registration link: https://clinicaltrials.gov/ct2/show/NCT01200212 Funding considerations: Roche Germany. Funders had no access to the study database and were not involved in analysis and interpretation of results **Author's name:** Sibylle Loibl **Institution:** Gynecologic Oncology Practice Hannover **Email:** Sibylle.Loibl@germanbreastgroup.de **Address:** Gynecologic Oncology Practice, HannoverHannover, Germany
Notes	All randomised patients were included in intention-to-treat analysis Study was terminated early due to futility

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	No explicit description of method of randomisation in text, but large multi-centre trial; presumed to use reasonable randomisation methods

TABEA *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No explicit description of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) Overall survival	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Progression-free survival (PFS)	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, assessed to be at high risk of bias because outcome can be subjective
Blinding of outcome assessment (detection bias) Overall response rate (ORR)	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, assessed to be at high risk of bias because outcome can be subjective
Blinding of outcome assessment (detection bias) Clinical benefit rate	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, assessed to be at high risk of bias because outcome can be subjective
Blinding of outcome assessment (detection bias) Toxicities	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, high risk of bias due to difference in toxicity profile
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited patients accounted for at each stage of analysis and included in ITT analysis
Selective reporting (reporting bias)	High risk	Clear outcomes delineated (PFS). Incomplete reporting of secondary outcomes, namely, CBR
Other bias	High risk	Study was terminated early due to pre-specified futility analysis. Additionally, patients were initially treated with docetaxel then paclitaxel due to change in licensing of taxane-bevacizumab. However, weekly paclitaxel is regarded as having efficacy similar to 3-weekly docetaxel

TACT2

Study characteristics	
Methods	Accrual time: 16 December 2005 to 5 December 2008 Multi-centre: United Kingdom Phase 3 open-label randomised controlled trial Median follow-up: 7.1 years Baseline comparability: balanced
Participants	N = 4391 patients (99.5% female) Age: median 51 years (range 45 to 59) Diagnosis: completely resected invasive breast cancer

TACT2 *(Continued)*

	Inclusion criteria: age ≥ 18 years; histologically confirmed invasive breast cancer (T0 to 3 N0 to 2 M0); adequate bone marrow, liver, and renal function Exclusion criteria: T4 disease; positive margins on final operative specimen; metastatic disease; other malignancy in previous 10 years (excluding DCIS, BCC, cervical carcinoma in situ) Notes: 53.2% had node-positive disease 60.8% were hormone receptor-positive, HER2-negative 12% were hormone receptor-positive, HER2-positive 6.9% were hormone receptor-negative, HER2-positive 19.7% were triple-negative
Interventions	Adjuvant setting ARM A (E-CMF): (N = 1116) epirubicin (100 mg/m^2 IV Day 1) every 3 weeks for 4 cycles followed by cyclophosphamide (600 mg/m^2 IV Day 1 and Day 8 or 100 mg/m^2 orally Days 1 to 14), methotrexate (40 mg/m^2 IV Day 1 and Day 8) and 5-fluorouracil (600 mg/m^2 IV Day 1 and Day 8) every 4 weeks for 4 cycles ARM B (ddE-CMF): (N = 1086) accelerated epirubicin (100 mg/m^2 IV Day 1 with pegfilgrastim 6 mg SC Day 2) every 2 weeks for 4 cycles followed by cyclophosphamide (600 mg/m^2 IV Day 1 and Day 8 or 100 mg/m^2 orally Days 1 to 14), methotrexate (40 mg/m^2 IV Day 1 and Day 8) and 5-fluorouracil (600 mg/m^2 IV Day 1 and Day 8) every 4 weeks for 4 cycles ARM C (E-X): (N = 1105) epirubicin (100 mg/m^2 IV Day 1) every 3 weeks for 4 cycles followed by capecitabine (1250 mg/m^2 orally Days 1 to 14) every 3 weeks for 4 cycles ARM D (ddE-X): (N = 1084) accelerated epirubicin (100 mg/m^2 IV Day 1 with pegfilgrastim 6 mg SC Day 2) every 2 weeks for 4 cycles followed by capecitabine (1250 mg/m^2 orally Days 1 to 14) every 3 weeks for 4 cycles
Outcomes	Primary: time to tumour recurrence (time from randomisation to first invasive relapse or breast cancer death) Secondary: overall survival (time from randomisation to death from any cause); invasive disease-free survival (time from randomisation to first invasive relapse, new second primary breast cancer, or death from any case); time to distant tumour recurrence (time from randomisation to first invasive distant relapse, excluding ipsilateral supraclavicular fossa, or to breast cancer death); tolerability (assessed by treatment adherence and frequency and nature of acute adverse events); quality of life
Identification	Trial registration link: https://clinicaltrials.gov/ct2/show/NCT00301925 Funding considerations: Cancer Research UK, Amgen, Pfizer, Roche **Corresponding author:** Prof David Cameron **Address:** Cancer Research UK Edinburgh Centre, MRC Institute of Genetics and Molecular Medicine, University of Edinburgh, Western General Hospital, Crewe Road South, Edinburgh EH4 2XR, UK **Email:** D.Cameron@ed.ac.uk
Notes	Intention-to-treat analysis was performed Males were included males (20/4391; 0.5%) Dose of fluorouracil was deemed different enough from capecitabine to be included in this study, despite the similarity between drugs

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Clear description of randomisation process; appropriate stratification factors
Allocation concealment (selection bias)	Low risk	Centralised randomisation with presumed allocation concealment

TACT2 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) Overall survival	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Disease-free survival (DFS)	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Toxicities	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, high risk due to difference in toxicity profile
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited patients accounted for at each stage of analysis and included in ITT analysis
Selective reporting (reporting bias)	Low risk	Adequate reporting of pre-specified outcomes
Other bias	Low risk	No other sources of bias detected

TURANDOT

Study characteristics	
Methods	Accrual time: 10 September 2008 to 30 August 2010 Multi-centre: Hungary, Israel, Austria, Romania, Czech Republic, Poland, Latvia, Bosnia and Herzegovina, Slovakia, Serbia, Bulgaria, Croatia (51 centres) Phase 3 open-label randomised controlled trial; non-inferiority study Median follow-up: 18.6 months Baseline comparability: balanced
Participants	N = 564 females Age: median age 59 years (range 48 to 65) Diagnosis: locally recurrent unresectable or metastatic HER2-negative breast cancer Inclusion criteria: age ≥ 18 years; histologically/cytologically confirmed HER2-negative breast adenocarcinoma; measurable or non-measurable locally recurrent or metastatic disease; candidate for chemotherapy; ECOG 0 to 2; life expectancy > 12 weeks; adequate baseline LVEF (> 50% by ECG or multiple-gated acquisition scan); adequate liver, renal, and haematological function; prior (neo)adjuvant chemotherapy allowed if completed > 6 months before randomisation or > 12 months if taxane-based and if maximum cumulative dose of anthracycline therapy did not exceed 360 mg/m^2 for doxorubicin or 720 mg/m^2 for epirubicin Exclusion criteria: HER2-positive disease; locally recurrent disease amenable to radiotherapy or resection with curative intent; previous chemotherapy for locally recurrent or metastatic breast cancer (previous hormonal therapy allowed); concomitant hormonal therapy; concomitant radiotherapy for local-

TURANDOT *(Continued)*

	ly recurrent or metastatic disease; CNS metastases; other primary tumours within the last 5 years except adequately controlled basal cell carcinoma of the skin or CIS of the cervix; uncontrolled hypertension; significant cardiovascular disease requiring medication or not controlled by medication Notes: 77% were hormone receptor-positive 0% were HER2-positive 23% were triple-negative
Interventions	First-line metastatic setting ARM 1 (BX): (N = 279) bevacizumab (15 mg/kg IV Day 1) plus capecitabine (1000 mg/m^2 twice daily oral Days 1 to 14) every 3 weeks until disease progression, toxicity, or withdrawal ARM 2 (BT): (N = 285) bevacizumab (10 mg/kg IV Day 1 and Day 15) plus paclitaxel (90 mg/m^2 IV Days 1, 8, and 15) every 4 weeks until disease progression, toxicity, or withdrawal Co-interventions were not reported Note: capecitabine starting dose was reduced by 25% if age ≥ 65 years
Outcomes	Primary: overall survival Secondary: objective response rate (RECIST); progression-free survival; time to response; duration of response; time to treatment failure; safety; quality of life (EORTC QLQ-C30)
Identification	Trial registration link: https://clinicaltrials.gov/ct2/show/NCT00600340 Funding considerations: sponsored by the Central European Cooperative Oncology. F. Hoffmann-La Roche (Basel, Switzerland) funded the trial. F. Hoffmann-La Roche had no role in design, conduct, or analysis of the trial, nor in interpretation of results or final content and decision to submit the manuscript for publication **Author's name:** Dr Christoph Zielinski **Institution:** Clinical Division of Oncology and Department of Medicine, Medical University of Vienna and CECOG, Waehringer Guertel 18-20, A-1090 Vienna, Austria **Email:** christoph.zielinski@meduniwien.ac.at **Address:** Clinical Division of Oncology and Department of Medicine I, Medical University of Vienna and CECOG, Waehringer Guertel 18-20, A-1090 Vienna, Austria
Notes	All randomised patients were included in intention-to-treat analysis Post-hoc retrospective analysis of outcomes based on hormone receptor and TNBC status

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised to treatment groups in a 1:1 ratio, with permuted blocks of size 6 stratified by clinically relevant stratification factors. No explicit comment as to actual randomisation process, but lage multi-centre study with presumed satisfactory randomisation process
Allocation concealment (selection bias)	Low risk	Allocated sequentially through an interactive web-based instrument integrated into an electronic data capture system

TURANDOT *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) Overall survival	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Progression-free survival (PFS)	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, assessed to be at high risk of bias because outcome can be subjective
Blinding of outcome assessment (detection bias) Overall response rate (ORR)	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, assessed to be at high risk of bias because outcome can be subjective
Blinding of outcome assessment (detection bias) Toxicities	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, high risk due to difference in toxicity profile
Blinding of outcome assessment (detection bias) Quality of life (QoL) - metastatic studies only	Unclear risk	Given the heterogeneity of treatment arms; both have clear pros and cons for quality of life. As this was an unblinded study and this outcome is subjective, this study was deemed to be at unclear risk
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited patients accounted for at each stage of analysis and included in ITT analysis
Selective reporting (reporting bias)	Low risk	Adequate reporting of pre-specified primary and secondary endpoints. Low risk except for quality of life, for which data were missing for later cycles; reasons unclear
Other bias	Low risk	No other sources of bias detected

USON 01062

Study characteristics	
Methods	Accrual time: August 2002 to February 2006 Multi-centre: United States Phase 3 open-label randomised controlled trial Median follow-up: 6.4 years Baseline comparability: balanced
Participants	N = 2611 females Age: median 50 years (range 26 to 72) for capecitabine arm; 51 (range 26 to 70) for comparator arm Diagnosis: completely resected invasive breast cancer

USON 01062 *(Continued)*

	Inclusion criteria: female; aged 18 to 70 years; ER and PR status determined; operable, histologically confirmed adenocarcinoma of the breast; negative surgical margins; ECOG 0 or 1; adequate wound healing; > 84 days since surgery; prior breast cancer allowed if diagnosed and resected > 5 years before entering the study - must have finished adjuvant hormonal treatment before study registration; adequate haematological, hepatic, and renal function; no evidence of metastatic disease on chest X-ray and bone scan; birth control if fertile (not OCP) Exclusion criteria: age > 70; any evidence of disease following surgical removal of primary tumour; stage IIIb or IV breast cancer; prior anthracycline, anthracenedione, or taxane therapy; prior treatment with 5-FU within the last 5 years; neoadjuvant therapy; peripheral neuropathy > grade 1; bilirubin > ULN; serious medical illness other that that treated by this study, which would limit survival to < 2 years; psychiatric condition that would prevent informed consent; uncontrolled or severe cardiovascular disease including recent MI or CCF; active uncontrolled infection; active hepatitis or HIV; uncontrolled disease such as diabetes; obese patients for whom the investigator is not comfortable administering full doses of study as calculated by BSA; concurrent immunotherapy; malignancy within past 5 years that could affect diagnosis or assessment of high-risk breast cancer; previous cancers involving an operation within 5 years before entering the study, not including skin (SCC, BCC) cancers and cervix cancer; history of hypersensitivity to docetaxel or other drugs formulated with polysorbate 80; lack of physical integrity of the upper GI tract, inability to swallow tablets, or a malabsorption syndrome; organ allograft; pregnant or breastfeeding Notes: 70% had node-positive disease 64% were hormone receptor-positive 12.8% were HER2-positive 29.9% were triple-negative
Interventions	Adjuvant setting ARM 1 (AC-XT): (N = 1307) doxorubicin (60 mg/m² IV Day 1) plus cyclophosphamide (600 mg/m² IV Day 1) every 3 weeks for 4 cycles followed by docetaxel (75 mg/m² IV Day 1) plus capecitabine (825 mg/m² twice daily oral Days 1 to 14) every 3 weeks for 4 cycles Capecitabine dose was originally 900 mg/m² twice daily, but the dose was reduced after the first interim safety analysis due to excessive toxicity ARM 2 (AC-T): (N = 1304) doxorubicin (60 mg/m² IV Day 1) plus cyclophosphamide (600 mg/m² IV Day 1) every 3 weeks for 4 cycles followed by docetaxel (100 mg/m² IV Day 1) every 3 weeks for 4 cycles Other adjuvant therapies Adjuvant trastuzumab was given to 31% of HER2-positive patients in capecitabine arm and 30% of HER2-positive patients in comparator arm Notes: Lower dose of docetaxel was used in combination with capecitabine (75 mg/m² vs 100 mg/m²)
Outcomes	Primary: disease-free survival**(**from randomisation until recurrence or death, whichever occurred first) Secondary: overall survival (from randomisation until death); safety
Identification	Trial registration link: https://clinicaltrials.gov/ct2/show/NCT00089479 Funding considerations: Hoffman-La Roche **Author's name:** Joyce O'Shaughnessy **Institution:** Baylor Charles A. Sammons Cancer Center

USON 01062 *(Continued)*

	Email: joyce.oshaughnessy@usoncology.com **Address:** Baylor Charles A. Sammons Cancer Center, 3535 Worth St., Collins Building, Dallas, TX 75246
Notes	Primary analysis was based on intention-to-treat population. Other analyses excluded patients who did not receive 2 cycles of both in AC and T/XT with > 50% planned dose of capecitabine

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised 1:1 centrally by USO research centrally
Allocation concealment (selection bias)	Low risk	Centralised randomisation with presumed allocation concealment but no explicit comment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) Overall survival	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Disease-free survival (DFS)	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Toxicities	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, high risk due to difference in toxicity profile
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited patients accounted for at each stage of analysis and included in ITT analysis
Selective reporting (reporting bias)	Low risk	Core primary and secondary endpoints stated and adhered to in reporting
Other bias	Low risk	No other sources of bias identified

Yoo 2015

Study characteristics

Methods	Accrual time: July 2005 to February 2010 Single-centre: Korea Phase 2 open-label randomised controlled trial Median follow-up: 53.7 months Baseline comparability: more grade 3 tumours in capecitabine arm (50% vs 31%), but otherwise balanced

Yoo 2015 *(Continued)*

Participants	N = 75 females Age: median 42 years (range 24 to 62) in capecitabine arm; 46 (range 27 to 70) in comparator arm Diagnosis: operable node-positive localised breast cancer Inclusion criteria: localised breast cancer; histologically or cytologically confirmed axillary nodal metastasis; age 18 to 70; ECOG 0 to 2; adequate haematological, renal, and hepatic function; locally advanced (> 5 cm diameter on ultrasound or MRI) and inflammatory breast cancer also eligible Exclusion criteria: previous treatment for breast cancer, including surgery, hormonal therapy, or chemotherapy; second primary malignancy (except carcinoma in situ of the cervix or adequately treated non-melanomatous skin cancer); distant metastasis; any serious concomitant medical disorder Notes: 100% were node-positive 54.7% had locally advanced disease (primary tumour > 5 cm) 28% had inflammatory breast cancer 54.7% were hormone receptor-positive 32% were HER2-positive 18.7% were triple-negative
Interventions	Neoadjuvant setting ARM 1 (CV-D): (N = 34) capecitabine (1000 mg/m^2 orally twice daily Days 1 to 14) plus vinorelbine (25 mg/m^2 IV Day 1 and Day 8) every 3 weeks for 4 cycles followed by docetaxel (75 mg/m^2 IV Day 1) every 3 weeks for 4 cycles followed by surgery ARM 2 (AC-D): (N = 39) doxorubicin (60 mg/m^2 IV Day 1) plus cyclophosphamide (600 mg/m^2 IV Day 1) every 3 weeks for 4 cycles followed by docetaxel (75 mg/m^2 IV Day 1) every 3 weeks for 4 cycles followed by surgery Other adjuvant therapies Prophylactic G-CSF was not permitted Adjuvant radiotherapy was given to patients with axillary lymph node-positive locally advanced or inflammatory breast cancer and those who underwent breast-conserving surgery Adjuvant hormonal therapy was given to patients with hormone receptor-positive disease 33% of HER2-positive patients received adjuvant trastuzumab
Outcomes	Primary: pathological complete response in the primary breast (complete absence of viable invasive tumour cells on postoperative pathological examination, regardless of residual carcinoma in situ) Secondary: radiological response rate; progression-free survival (time from date of study enrolment to first date of progressive disease or death from any cause); overall survival (time from date of study enrolment to date of death from any cause); safety profile
Identification	Funding considerations: no conflicts of interest declared **Corresponding author:** Jin-Hee Ahn; Department of Oncology, Asan Medical Centre, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 138-736, Korea; Ph: 82-2-3010-3210; Fax: 82-2-3010-6961 Email: drjiny@amc.seoul.kr

Yoo 2015 *(Continued)*

Notes	All randomised patients were included in intention-to-treat analysis Hazard ratios were calculated by Tierney method and Plot digitiser

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomisation process not specified; small single-centre phase 2 study; randomised 1:1 with appropriate stratification factors
Allocation concealment (selection bias)	High risk	Single-centre study; small numbers; no sequence allocation described; higher chance of poor concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) Overall survival	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Disease-free survival (DFS)	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Pathologic complete response (pCR) - neoadjuvant studies only	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Toxicities	High risk	Given unblinded study, high risk due to difference in toxicity profile
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited patients accounted for at each stage of analysis and included in ITT analysis
Selective reporting (reporting bias)	Low risk	Adequate reporting of pre-specified primary and secondary endpoints
Other bias	Low risk	No other sources of bias detected

Zhang 2016

Study characteristics

Methods	Accrual time: January 2011 to December 2013 Multi-centre: single centre Phase 3 open-label randomised trial Median follow-up: not reported Baseline comparability: appear balanced between groups

Zhang 2016 *(Continued)*

Participants	N = 131 females Age: median XEC 43 (19 to 68), FEC 42 (21 to 69) Diagnosis: newly diagnosed, biopsy-proven, stage II/III operable breast cancer with axillary LN involvement Inclusion criteria: operable breast cancer defined as tumour with diameter > 1 cm diagnosed by ultrasonography or magnetic resonance imaging (MRI); histologically or cytologically confirmed axillary nodal metastasis; age 18 to 70; ECOG performance status ≤ 1; adequate haematological, renal, cardiac, and hepatic function Exclusion criteria: prior surgery, hormonal treatment, chemotherapy, or radiotherapy; history of cancer except for in situ uterine cervical cancer or non-melanotic skin cancer; any distant metastasis; any serious concomitant systemic disorder Notes: 77% were IDC 64% were hormone receptor-positive 29% were HER2-positive
Interventions	Neoadjuvant ARM 1 (XEC): (N = 61) capecitabine 1000 mg/m^2 given orally twice a day for 14 days of every-3-week cycle + epirubicin 100 mg/m^2 + cyclophosphamide 500 mg/m^2 given intravenously on Day 1 every 3 weeks for 4 cycles ARM 2 (FEC): (N = 70) 5-FU 500mg/m^2 + epirubicin 100 mg/m^2 + cyclophosphamide 500 mg/m^2 given intravenously on Day 1 every 3 weeks for 4 cycles No mention of use of G-CSF
Outcomes	Primary: pathological complete response Secondary: overall response rate, safety
Identification	Funding considerations: no conflicts of interest listed **Author's name:** Jianlun Liu **Institution:** Affiliated Tumour Hospital of Guangxi Medical University **Email:** jianlunliu@hotmail.com **Address:** Department of Breast Surgery, Affiliated Tumor Hospital of Guangxi Medical University, 71 Hedi Road, Nanning 530021, Guangxi, People's Republic of China
Notes	All randomised patients were included in intention-to-treat analysis Study was designed for neoadjuvant XEC - adjuvant XT vs neoadjuvant FEC - adjuvant T Adjuvant outcomes (DFS, OS) were not yet reported Dose of fluorouracil was deemed different enough from capecitabine for inclusion in this study, despite the similarity between drugs

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomisation process not specified; small single-centre phase 2 study; randomised 1:1 with appropriate stratification factors
Allocation concealment (selection bias)	High risk	Single-centre study; small numbers; no sequence allocation described; higher chance of poor concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study

Zhang 2016 *(Continued)*

Blinding of outcome assessment (detection bias) Pathologic complete response (pCR) - neoadjuvant studies only	Low risk	No explicit comment in the report as to blinding of outcome assessment. Low risk of bias because outcome unlikely to be affected by lack of blinding
Blinding of outcome assessment (detection bias) Toxicities	High risk	No explicit comment as to blinding of outcome assessment. Given unblinded study, high risk due to difference in toxicity profile
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited patients accounted for at each stage of analysis and included in ITT analysis
Selective reporting (reporting bias)	Low risk	Adequate reporting of pre-specified primary and secondary endpoints
Other bias	Low risk	No other sources of bias detected

5-FU: 5-fluorouracil.
ALND: axillary lymph node dissection.
BC: breast cancer.
BCC: basal cell carcinoma.
CBR: clinical benefit rate.
CCF: congestive cardiac failure.
CIS: carcinoma in situ.
CNS: central nervous system.
DFS: disease-free survival.
EBC: exhaled breath condensate.
ECG: electrocardiogram.
ECOG: Eastern Cooperative Oncology Group.
EGFR: epidermal growth factor receptor.
EORTC QLQ-C30: European Organization for Research and Treatment of Cancer core quality of life questionnaire.
ER: oestrogen receptor.
FACT-B: Functional Assessment of Cancer Therapy - Breast.
G-CSF: granulocyte colony-stimulating factor.
gpNMB: glycoprotein NMB.
HER2: human epidermal growth factor receptor 2.
IHC: immunohistochemistry.
ITT: intention-to-treat.
LVEF: left ventricular ejection fraction.
MI: myocardial infarction.
NYHA: New York Heart Association.
OCP: oral contraceptive pill.
ORR: objective response rate.
OS: overall survival.
pCR: pathological complete response.
PFS: progression-free survival.
PR: partial response.
QoL: quality of life.
RECIST: Response Evaluation Criteria in Solid Tumours.
SCC: squamous cell carcinoma.
SD: stable disease.
TNBC: triple-negative breast cancer.
TtP: time to progression.
ULN: upper limit of normal.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACTRN12613000206729	RCT: currently open and in accrual
AHX-03-202	Wrong comparator
ANZ 0001	No outcome data by hormone receptor status
Berton Rigaud 2008	Wrong comparator: capecitabine vs fluorouracil
Beslija 2006	No outcome data by hormone receptor status
CALBG 49907	Wrong comparator: capecitabine vs fluorouracil or anthracycline (physician's choice)
Campone 2009	Wrong study design
ECTO-II	Wrong intervention
EMBRACE	Study did not report outcome data by HR status This was a study of eribulin (508) vs physician's choice (238) chemotherapy, in which only a few patients were given capecitabine (44 patients). Subsequent outcomes by HR status were reported, but only as part of a pooled analysis (Pivot 2016)
EORTC 10001	No outcome data by hormone receptor status
ERASME-4	No outcome data by hormone receptor status
Eremin 2015	No outcome data by hormone receptor status
EudraCT 2010-022646-24	No published results
GAIN	No outcome data by hormone receptor status
Gemcitabin 02 MC	No outcome data by hormone receptor status
Genta Incorporated 2012	No published results
Georgia CORE	Wrong study design
GEPARTRIO	No outcome data by hormone receptor status
Ghosn 2009	No outcome data by hormone receptor status
Giacchetti 2011	No outcome data by hormone receptor status
GLICO-0801	No outcome data by hormone receptor status
Gruppo	Duplicate citation
HellenicOncologyResearch-Group 2007	RCT: study terminated early with no reported outcome data
HenriRoche 2006	Wrong comparator
Hoffman 2004	Wrong study design

Study	Reason for exclusion
Hoffmann LaRoche 2015	RCT: no reported outcome data
HORG CT/02.09	No outcome data by hormone receptor status
Hu 2010	No outcome data by hormone receptor status
Hudis 2011	Wrong comparator
ICE-II	No outcome data by hormone receptor status
ID01-580	No outcome data by hormone receptor status
Istituto Europeo di Oncologia 2006	RCT: no reported outcome data
JBCRN 05	Wrong comparator
Kourlaba 2014	Irrelevant
Lam	No outcome data by hormone receptor status
LiNanlin 2013	RCT: currently open and in accrual
Lindner 2015	Duplicate citation
Loman 2016	RCT: currently open and in accrual
MAMMA-3	No outcome data by hormone receptor status
Mansutti 2008	No outcome data by hormone receptor status
Martin 2015	Wrong comparator: capecitabine vs non-chemotherapy comparator
Matter-Walstra 2015	No outcome data by hormone receptor status
Mavroudis 2006	Duplicate citation
Melisko 2016	Wrong comparator: capecitabine vs non-chemotherapy comparator
Mobarek 2009	No outcome data by hormone receptor status
Moiseenko 2000a	No outcome data by hormone receptor status
Nagayama 2012	Wrong comparator
NCT00081796	RCT: no reported outcome data
NCT00082095	No outcome data by hormone receptor status
NCT01112826	RCT: currently open and in accrual
NCT01354522	RCT: status unknown
NCT01415336	RCT: status unknown

Study	Reason for exclusion
NCT01655992	Wrong comparator: capecitabine vs fluorouracil
NCT01869192	Wrong study design
NCT02207335	RCT: currently open and in accrual
NCT02767661	RCT: currently open and in accrual
NorCap-CA223	No outcome data by hormone receptor status
O'Shaughnessy 2001	No outcome data by hormone receptor status
OMEGA	No outcome data by hormone receptor status
OOTR N003	No outcome data by hormone receptor status
Pegram 2005	Wrong comparator
PELICAN	No outcome data by hormone receptor status
Pivot 2016	Review paper/meta-analysis
RIBBON-1	No outcome data by hormone receptor status
RIBBON-2	No outcome data by hormone receptor status
Rivera 2012	Wrong comparator
Rivera Rodriguez 2013	No outcome data by hormone receptor status
Roche 2006	Duplicate citation
Rugo 2008	Wrong study design
SAKK 24/09	No outcome data by hormone receptor status
Sato 2012	No outcome data by hormone receptor status
Schneeweiss 2013	Wrong study design
Shao 2010	Wrong comparator
Soto 2006	Wrong study design
TANIA	Wrong study design
TEX	No outcome data by hormone receptor status
VITAL	No outcome data by hormone receptor status
Wang 2014	No outcome data by hormone receptor status
Wang 2015	Wrong comparator
XeNA	Wrong study design

Study	Reason for exclusion
Yamamoto 2014	Wrong comparator
Yang 2013	No outcome data by hormone receptor status
Yardley 2015	Wrong comparator: capecitabine vs non-chemotherapy comparator
Yoshinami 2013	No published results
Yu 2011	Wrong comparator
Zhang 2015	No outcome by hormone receptor status

RCT: randomised controlled trial.

DATA AND ANALYSES

Comparison 1. Metastatic all: capecitabine-containing regimen vs non-capecitabine-containing regimen

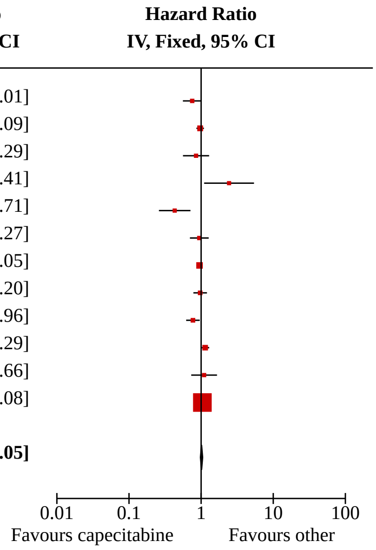
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 OS all	12	4325	Hazard Ratio (IV, Fixed, 95% CI)	1.01 [0.98, 1.05]
1.2 OS hormone receptor-positive: sensitivity analysis of pooled analysis	7	2036	Hazard Ratio (IV, Fixed, 95% CI)	0.93 [0.84, 1.04]
1.2.1 All studies excluding pooled analysis	6	1565	Hazard Ratio (IV, Fixed, 95% CI)	0.90 [0.80, 1.02]
1.2.2 Pooled analysis	1	471	Hazard Ratio (IV, Fixed, 95% CI)	1.04 [0.83, 1.30]
1.3 OS hormone receptor-negative: sensitivity analysis of pooled analysis	8	1663	Hazard Ratio (IV, Fixed, 95% CI)	1.00 [0.88, 1.13]
1.3.1 All studies excluding pooled analysis	7	1408	Hazard Ratio (IV, Fixed, 95% CI)	1.05 [0.91, 1.20]
1.3.2 Pooled analysis	1	255	Hazard Ratio (IV, Fixed, 95% CI)	0.83 [0.62, 1.10]
1.6 OS triple-negative	5	840	Hazard Ratio (IV, Fixed, 95% CI)	1.20 [1.01, 1.43]
1.7 PFS all	12	4325	Hazard Ratio (IV, Fixed, 95% CI)	0.89 [0.82, 0.95]
1.8 PFS hormone receptor-positive: sensitivity analysis of pooled analysis	7	1843	Hazard Ratio (IV, Fixed, 95% CI)	0.82 [0.73, 0.91]
1.8.1 All studies excluding pooled analysis	6	1372	Hazard Ratio (IV, Fixed, 95% CI)	0.77 [0.68, 0.87]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.8.2 Pooled analysis	1	471	Hazard Ratio (IV, Fixed, 95% CI)	0.95 [0.78, 1.17]
1.9 PFS hormone receptor-negative: sensitivity analysis of pooled analysis	7	1155	Hazard Ratio (IV, Fixed, 95% CI)	0.96 [0.83, 1.10]
1.9.1 All studies excluding pooled analysis	6	900	Hazard Ratio (IV, Fixed, 95% CI)	1.01 [0.85, 1.19]
1.9.2 Pooled analysis	1	255	Hazard Ratio (IV, Fixed, 95% CI)	0.84 [0.64, 1.10]
1.12 PFS triple-negative	5	840	Hazard Ratio (IV, Fixed, 95% CI)	1.22 [1.04, 1.44]
1.13 ORR all	12	4200	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.84, 1.11]
1.14 ORR TNBC	3	462	Odds Ratio (M-H, Fixed, 95% CI)	0.42 [0.27, 0.65]
1.15 CBR all	4	1546	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.76, 1.21]
1.16 Complete response rate all	6	2242	Odds Ratio (M-H, Fixed, 95% CI)	1.36 [0.85, 2.18]
1.17 Complete response rate HR+	2	295	Odds Ratio (M-H, Fixed, 95% CI)	4.75 [1.17, 19.33]
1.18 Complete response rate HR-	2	186	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.39, 1.73]

Analysis 1.1. Comparison 1: Metastatic all: capecitabine-containing regimen vs non-capecitabine-containing regimen, Outcome 1: OS all

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI
BOLERO6 (1)	-0.2852	0.1515	102	104	1.2%	0.75 [0.56 , 1.01]
Chan 2009 (2)	-0.0305	0.0614	152	153	7.6%	0.97 [0.86 , 1.09]
CHAT	-0.1625	0.2129	112	110	0.6%	0.85 [0.56 , 1.29]
Fan 2013 (1)	0.8916	0.4063	26	27	0.2%	2.44 [1.10 , 5.41]
IMELDA	-0.844	0.2567	91	94	0.4%	0.43 [0.26 , 0.71]
METRIC (1)	-0.0583	0.1528	109	218	1.2%	0.94 [0.70 , 1.27]
Pallis 2012 (1)	-0.0511	0.0513	74	74	10.8%	0.95 [0.86 , 1.05]
Seidman 2011 (3)	-0.0305	0.1104	236	239	2.3%	0.97 [0.78 , 1.20]
SO140999	-0.2614	0.1105	255	256	2.3%	0.77 [0.62 , 0.96]
Study 301 (1)	0.129	0.0658	548	554	6.6%	1.14 [1.00 , 1.29]
TABEA	0.0953	0.2099	111	116	0.6%	1.10 [0.73 , 1.66]
TURANDOT	0.0392	0.0208	279	285	66.0%	1.04 [1.00 , 1.08]
Total (95% CI)			**2095**	**2230**	**100.0%**	**1.01 [0.98 , 1.05]**

Heterogeneity: Chi² = 33.83, df = 11 (P = 0.0004); I² = 67%
Test for overall effect: Z = 0.76 (P = 0.44)
Test for subgroup differences: Not applicable

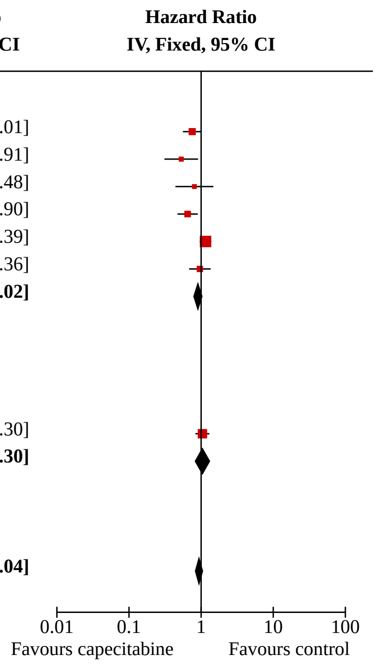


Footnotes
(1) HR inverted from published data
(2) HR calculated using Revman calculator
(3) HR inverted from reported data

Analysis 1.2. Comparison 1: Metastatic all: capecitabine-containing regimen vs non-capecitabine-containing regimen, Outcome 2: OS hormone receptor-positive: sensitivity analysis of pooled analysis

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
1.2.1 All studies excluding pooled analysis						
BOLERO6 (1)	-0.2852	0.1515	102	104	13.6%	0.75 [0.56 , 1.01]
IMELDA	-0.6349	0.2736	66	73	4.2%	0.53 [0.31 , 0.91]
Pallis 2012	-0.2152	0.3091	44	38	3.3%	0.81 [0.44 , 1.48]
SO140999	-0.4308	0.1654	90	95	11.4%	0.65 [0.47 , 0.90]
Study 301 (1)	0.1404	0.0965	278	259	33.5%	1.15 [0.95 , 1.39]
TURANDOT	-0.0408	0.1759	201	215	10.1%	0.96 [0.68 , 1.36]
Subtotal (95% CI)			**781**	**784**	**76.0%**	**0.90 [0.80 , 1.02]**
Heterogeneity: Chi² = 15.77, df = 5 (P = 0.008); I² = 68%						
Test for overall effect: Z = 1.61 (P = 0.11)						
1.2.2 Pooled analysis						
Seidman 2011 (2)	0.0408	0.1139	238	233	24.0%	1.04 [0.83 , 1.30]
Subtotal (95% CI)			**238**	**233**	**24.0%**	**1.04 [0.83 , 1.30]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.36 (P = 0.72)						
Total (95% CI)			**1019**	**1017**	**100.0%**	**0.93 [0.84 , 1.04]**

Heterogeneity: Chi² = 16.99, df = 6 (P = 0.009); I² = 65%
Test for overall effect: Z = 1.23 (P = 0.22)
Test for subgroup differences: Chi² = 1.21, df = 1 (P = 0.27), I² = 17.7%

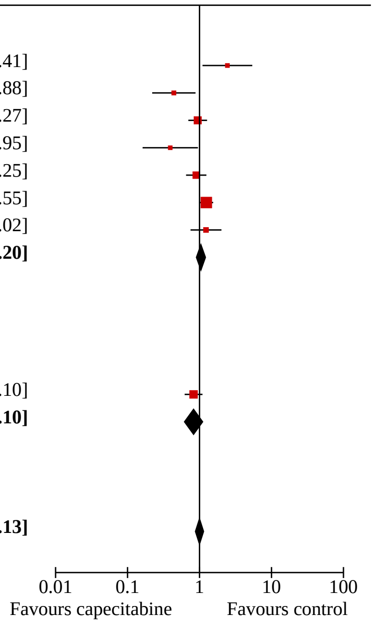


Footnotes
(1) HR inverted from published data
(2) Data from pooled analysis (Seidman 2014) as outcomes by hormone receptor status not reported in primary papers. HR inverted from published data.

Analysis 1.3. Comparison 1: Metastatic all: capecitabine-containing regimen vs non-capecitabine-containing regimen, Outcome 3: OS hormone receptor-negative: sensitivity analysis of pooled analysis

Study or Subgroup	log[Hazard Ratio]	SE	Experimental Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
1.3.1 All studies excluding pooled analysis						
Fan 2013 (1)	0.8916	0.4063	26	27	2.5%	2.44 [1.10 , 5.41]
IMELDA	-0.821	0.3537	25	21	3.3%	0.44 [0.22 , 0.88]
METRIC (1)	-0.0583	0.1528	109	218	17.7%	0.94 [0.70 , 1.27]
Pallis 2012	-0.9365	0.4516	10	17	2.0%	0.39 [0.16 , 0.95]
SO140999	-0.1054	0.166	88	83	15.0%	0.90 [0.65 , 1.25]
Study 301 (1)	0.2182	0.1113	216	233	33.4%	1.24 [1.00 , 1.55]
TURANDOT	0.207	0.2524	168	167	6.5%	1.23 [0.75 , 2.02]
Subtotal (95% CI)			**642**	**766**	**80.5%**	**1.05 [0.91 , 1.20]**
Heterogeneity: Chi² = 19.17, df = 6 (P = 0.004); I² = 69%						
Test for overall effect: Z = 0.63 (P = 0.53)						
1.3.2 Pooled analysis						
Seidman 2011 (2)	-0.1906	0.1457	119	136	19.5%	0.83 [0.62 , 1.10]
Subtotal (95% CI)			**119**	**136**	**19.5%**	**0.83 [0.62 , 1.10]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						
Total (95% CI)			**761**	**902**	**100.0%**	**1.00 [0.88 , 1.13]**
Heterogeneity: Chi² = 21.28, df = 7 (P = 0.003); I² = 67%						
Test for overall effect: Z = 0.01 (P = 0.99)						
Test for subgroup differences: Chi² = 2.11, df = 1 (P = 0.15), I² = 52.6%						

Hazard Ratio
IV, Fixed, 95% CI



Footnotes

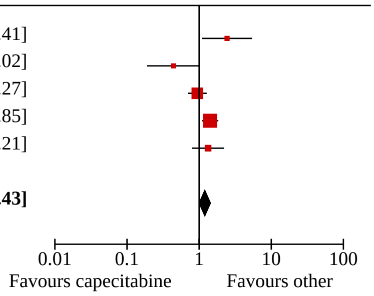
(1) HR inverted from published data

(2) Data from pooled analysis (Seidman 2014) as outcomes by hormone receptor status not reported in primary papers. HR inverted from published data.

Analysis 1.6. Comparison 1: Metastatic all: capecitabine-containing regimen vs non-capecitabine-containing regimen, Outcome 6: OS triple-negative

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Fan 2013 (1)	0.8916	0.4063	26	27	4.8%	2.44 [1.10 , 5.41]
IMELDA	-0.821	0.4285	25	21	4.3%	0.44 [0.19 , 1.02]
METRIC (1)	-0.0583	0.1528	109	218	33.9%	0.94 [0.70 , 1.27]
Study 301 (1)	0.3538	0.1324	134	150	45.2%	1.42 [1.10 , 1.85]
TURANDOT	0.2852	0.2594	67	63	11.8%	1.33 [0.80 , 2.21]
Total (95% CI)			**361**	**479**	**100.0%**	**1.20 [1.01 , 1.43]**
Heterogeneity: Chi² = 12.84, df = 4 (P = 0.01); I² = 69%						
Test for overall effect: Z = 2.03 (P = 0.04)						
Test for subgroup differences: Not applicable						

Hazard Ratio
IV, Fixed, 95% CI



Footnotes

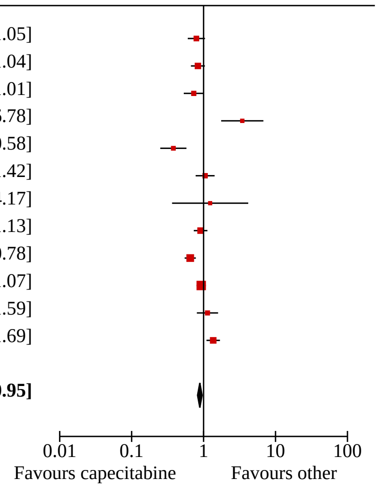
(1) HR inverted from published data

Analysis 1.7. Comparison 1: Metastatic all: capecitabine-containing regimen vs non-capecitabine-containing regimen, Outcome 7: PFS all

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI
BOLERO6 (1)	-0.2311	0.1407	102	104	6.9%	0.79 [0.60 , 1.05]
Chan 2009 (1)	-0.1823	0.1139	152	153	10.5%	0.83 [0.67 , 1.04]
CHAT	-0.3147	0.1634	112	110	5.1%	0.73 [0.53 , 1.01]
Fan 2013 (1)	1.2379	0.3448	26	27	1.1%	3.45 [1.75 , 6.78]
IMELDA	-0.9676	0.2136	91	94	3.0%	0.38 [0.25 , 0.58]
METRIC (1)	0.0488	0.1548	109	218	5.7%	1.05 [0.78 , 1.42]
Pallis 2012	0.2097	0.622	74	74	0.4%	1.23 [0.36 , 4.17]
Seidman 2011	-0.0962	0.1115	236	239	11.0%	0.91 [0.73 , 1.13]
SO140999	-0.4277	0.0915	255	256	16.3%	0.65 [0.54 , 0.78]
Study 301 (1)	-0.076	0.0751	548	554	24.2%	0.93 [0.80 , 1.07]
TABEA	0.124	0.1733	111	116	4.5%	1.13 [0.81 , 1.59]
TURANDOT	0.3075	0.11	279	285	11.3%	1.36 [1.10 , 1.69]
Total (95% CI)			**2095**	**2230**	**100.0%**	**0.89 [0.82 , 0.95]**

Heterogeneity: Chi² = 63.85, df = 11 (P < 0.00001); I² = 83%
Test for overall effect: Z = 3.27 (P = 0.001)
Test for subgroup differences: Not applicable

Hazard Ratio IV, Fixed, 95% CI



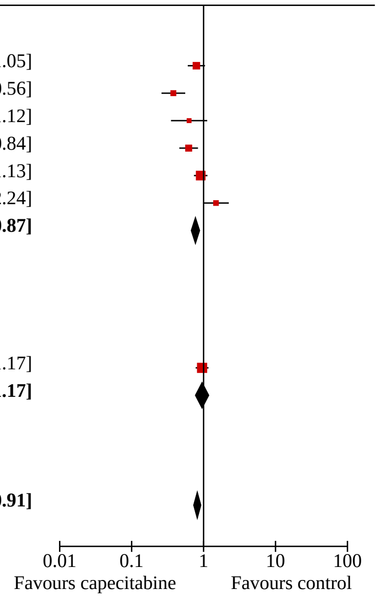
Footnotes
(1) HR inverted from published data

Analysis 1.8. Comparison 1: Metastatic all: capecitabine-containing regimen vs non-capecitabine-containing regimen, Outcome 8: PFS hormone receptor-positive: sensitivity analysis of pooled analysis

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
1.8.1 All studies excluding pooled analysis						
BOLERO6 (1)	-0.2311	0.1407	102	104	15.4%	0.79 [0.60 , 1.05]
IMELDA	-0.9676	0.1936	66	73	8.1%	0.38 [0.26 , 0.56]
Pallis 2012	-0.4638	0.2959	44	38	3.5%	0.63 [0.35 , 1.12]
SO140999	-0.478	0.1523	90	95	13.1%	0.62 [0.46 , 0.84]
Study 301 (1)	-0.0926	0.1099	305	279	25.2%	0.91 [0.73 , 1.13]
TABEA	0.3967	0.2091	86	90	7.0%	1.49 [0.99 , 2.24]
Subtotal (95% CI)			**693**	**679**	**72.4%**	**0.77 [0.68 , 0.87]**
Heterogeneity: Chi² = 28.11, df = 5 (P < 0.0001); I² = 82%						
Test for overall effect: Z = 4.02 (P < 0.0001)						
1.8.2 Pooled analysis						
Seidman 2011 (2)	-0.0488	0.105	238	233	27.6%	0.95 [0.78 , 1.17]
Subtotal (95% CI)			**238**	**233**	**27.6%**	**0.95 [0.78 , 1.17]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.64)						
Total (95% CI)			**931**	**912**	**100.0%**	**0.82 [0.73 , 0.91]**

Heterogeneity: Chi² = 31.07, df = 6 (P < 0.0001); I² = 81%
Test for overall effect: Z = 3.67 (P = 0.0002)
Test for subgroup differences: Chi² = 2.96, df = 1 (P = 0.09), I² = 66.2%

Hazard Ratio IV, Fixed, 95% CI

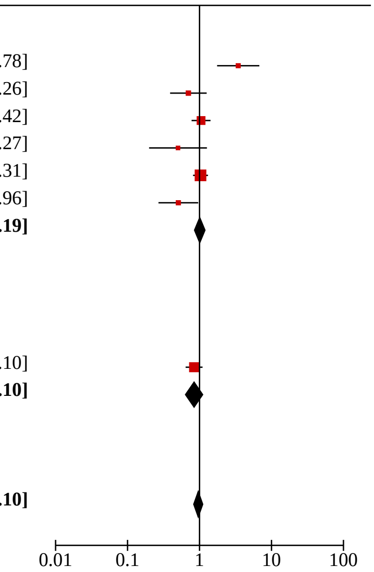


Footnotes
(1) HR inverted from published data
(2) Data from pooled analysis (Seidman 2014) as outcomes by hormone receptor status not reported in primary papers. HR inverted from reported data.

Analysis 1.9. Comparison 1: Metastatic all: capecitabine-containing regimen vs non-capecitabine-containing regimen, Outcome 9: PFS hormone receptor-negative: sensitivity analysis of pooled analysis

Study or Subgroup	log[Hazard Ratio]	SE	Experimental Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
1.9.1 All studies excluding pooled analysis						
Fan 2013 (1)	1.2379	0.3448	26	27	4.3%	3.45 [1.75 , 6.78]
IMELDA	-0.3567	0.2984	25	21	5.7%	0.70 [0.39 , 1.26]
METRIC (1)	0.0488	0.1548	109	218	21.4%	1.05 [0.78 , 1.42]
Pallis 2012	-0.6882	0.4721	10	17	2.3%	0.50 [0.20 , 1.27]
Study 301 (1)	0.0315	0.1217	184	212	34.6%	1.03 [0.81 , 1.31]
TABEA	-0.6775	0.3243	25	26	4.9%	0.51 [0.27 , 0.96]
Subtotal (95% CI)			**379**	**521**	**73.2%**	**1.01 [0.85 , 1.19]**
Heterogeneity: Chi² = 20.97, df = 5 (P = 0.0008); I² = 76%						
Test for overall effect: Z = 0.09 (P = 0.93)						
1.9.2 Pooled analysis						
Seidman 2011 (2)	-0.174	0.1381	119	136	26.8%	0.84 [0.64 , 1.10]
Subtotal (95% CI)			**119**	**136**	**26.8%**	**0.84 [0.64 , 1.10]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.26 (P = 0.21)						
Total (95% CI)			**498**	**657**	**100.0%**	**0.96 [0.83 , 1.10]**
Heterogeneity: Chi² = 22.23, df = 6 (P = 0.001); I² = 73%						
Test for overall effect: Z = 0.58 (P = 0.56)						
Test for subgroup differences: Chi² = 1.26, df = 1 (P = 0.26), I² = 20.7%						

Hazard Ratio
IV, Fixed, 95% CI



Footnotes

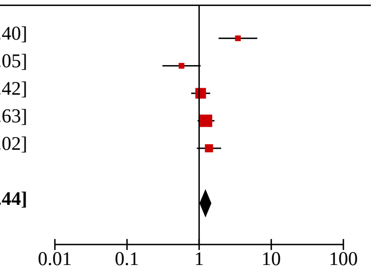
(1) HR inverted from published data

(2) Data from pooled analysis (Seidman 2014) as outcomes by hormone receptor status not reported in primary papers. HR inverted from reported data.

Analysis 1.12. Comparison 1: Metastatic all: capecitabine-containing regimen vs non-capecitabine-containing regimen, Outcome 12: PFS triple-negative

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Fan 2013 (1)	1.2384	0.3152	26	27	7.2%	3.45 [1.86 , 6.40]
IMELDA	-0.5621	0.3108	25	21	7.4%	0.57 [0.31 , 1.05]
METRIC (1)	0.0488	0.1548	109	218	29.7%	1.05 [0.78 , 1.42]
Study 301 (1)	0.2206	0.1375	134	150	37.6%	1.25 [0.95 , 1.63]
TURANDOT	0.3148	0.1976	67	63	18.2%	1.37 [0.93 , 2.02]
Total (95% CI)			**361**	**479**	**100.0%**	**1.22 [1.04 , 1.44]**
Heterogeneity: Chi² = 18.18, df = 4 (P = 0.001); I² = 78%						
Test for overall effect: Z = 2.40 (P = 0.02)						
Test for subgroup differences: Not applicable						

Hazard Ratio
IV, Fixed, 95% CI



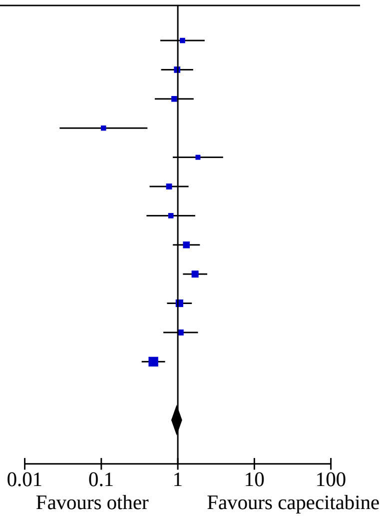
Footnotes

(1) HR inverted from published data

Analysis 1.13. Comparison 1: Metastatic all: capecitabine-containing regimen vs non-capecitabine-containing regimen, Outcome 13: ORR all

Study or Subgroup	Capecitabine Events	Capecitabine Total	Other Events	Other Total	Weight	Odds Ratio M-H, Fixed, 95% CI
BOLERO6	23	102	21	104	4.1%	1.15 [0.59 , 2.24]
Chan 2009	48	152	49	153	8.4%	0.98 [0.60 , 1.59]
CHAT	79	112	80	110	6.0%	0.90 [0.50 , 1.61]
Fan 2013	4	26	17	27	3.6%	0.11 [0.03 , 0.40]
IMELDA	78	91	72	94	2.6%	1.83 [0.86 , 3.91]
METRIC	21	100	46	179	6.6%	0.77 [0.43 , 1.38]
Pallis 2012	18	74	21	74	4.0%	0.81 [0.39 , 1.69]
Seidman 2011	78	191	72	207	10.3%	1.29 [0.86 , 1.94]
SO140999	107	255	77	256	11.3%	1.68 [1.17 , 2.42]
Study 301	63	548	61	554	13.6%	1.05 [0.72 , 1.53]
TABEA	55	111	55	116	6.9%	1.09 [0.65 , 1.83]
TURANDOT	76	279	125	285	22.7%	0.48 [0.34 , 0.68]
Total (95% CI)		**2041**		**2159**	**100.0%**	**0.97 [0.84 , 1.11]**
Total events:	650		696			

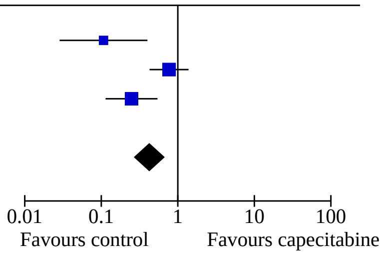
Heterogeneity: Chi² = 40.97, df = 11 (P < 0.0001); I² = 73%
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable



Analysis 1.14. Comparison 1: Metastatic all: capecitabine-containing regimen vs non-capecitabine-containing regimen, Outcome 14: ORR TNBC

Study or Subgroup	Capecitabine Events	Capecitabine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Fan 2013	4	26	17	27	21.4%	0.11 [0.03 , 0.40]
METRIC	21	100	46	179	39.5%	0.77 [0.43 , 1.38]
TURANDOT	13	67	31	63	39.1%	0.25 [0.11 , 0.54]
Total (95% CI)		**193**		**269**	**100.0%**	**0.42 [0.27 , 0.65]**
Total events:	38		94			

Heterogeneity: Chi² = 9.92, df = 2 (P = 0.007); I² = 80%
Test for overall effect: Z = 3.88 (P = 0.0001)
Test for subgroup differences: Not applicable

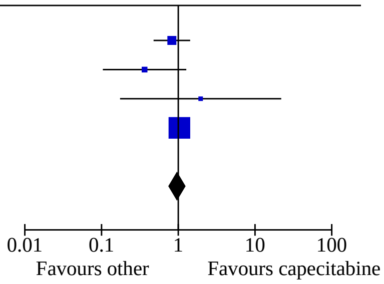


Analysis 1.15. Comparison 1: Metastatic all: capecitabine-containing regimen vs non-capecitabine-containing regimen, Outcome 15: CBR all

Study or Subgroup	Capecitabine Events	Capecitabine Total	Other Events	Other Total	Weight	Odds Ratio M-H, Fixed, 95% CI
BOLERO6	53	102	59	104	19.6%	0.82 [0.48 , 1.43]
Fan 2013	16	26	22	27	5.8%	0.36 [0.10 , 1.27]
IMELDA	90	91	92	94	0.7%	1.96 [0.17 , 21.96]
Study 301	147	548	145	554	73.9%	1.03 [0.79 , 1.35]
Total (95% CI)		**767**		**779**	**100.0%**	**0.96 [0.76 , 1.21]**
Total events:	306		318			

Heterogeneity: Chi² = 3.23, df = 3 (P = 0.36); I² = 7%
Test for overall effect: Z = 0.34 (P = 0.74)
Test for subgroup differences: Not applicable

Odds Ratio
M-H, Fixed, 95% CI

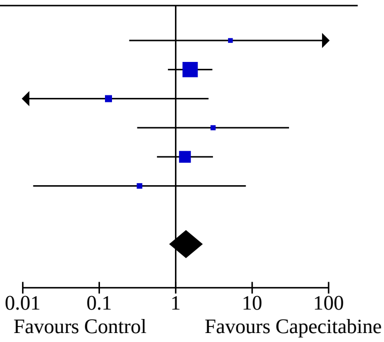


Analysis 1.16. Comparison 1: Metastatic all: capecitabine-containing regimen vs non-capecitabine-containing regimen, Outcome 16: Complete response rate all

Study or Subgroup	Capecitabine Events	Capecitabine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
BOLERO6	2	102	0	104	1.6%	5.20 [0.25 , 109.63]
CHAT	26	112	18	110	46.9%	1.55 [0.79 , 3.02]
Fan 2013	0	26	3	27	11.3%	0.13 [0.01 , 2.69]
Pallis 2012	3	74	1	74	3.2%	3.08 [0.31 , 30.36]
SO140999	13	255	10	256	31.9%	1.32 [0.57 , 3.07]
Study 301	0	548	1	554	5.0%	0.34 [0.01 , 8.28]
Total (95% CI)		**1117**		**1125**	**100.0%**	**1.36 [0.85 , 2.18]**
Total events:	44		33			

Heterogeneity: Chi² = 4.41, df = 5 (P = 0.49); I² = 0%
Test for overall effect: Z = 1.28 (P = 0.20)
Test for subgroup differences: Not applicable

Odds Ratio
M-H, Fixed, 95% CI

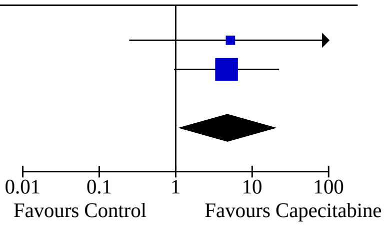


Analysis 1.17. Comparison 1: Metastatic all: capecitabine-containing regimen vs non-capecitabine-containing regimen, Outcome 17: Complete response rate HR+

Study or Subgroup	Capecitabine Events	Capecitabine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
BOLERO6	2	102	0	104	21.2%	5.20 [0.25 , 109.63]
CHAT	10	50	2	39	78.8%	4.63 [0.95 , 22.51]
Total (95% CI)		**152**		**143**	**100.0%**	**4.75 [1.17 , 19.33]**
Total events:	12		2			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 2.17 (P = 0.03)
Test for subgroup differences: Not applicable

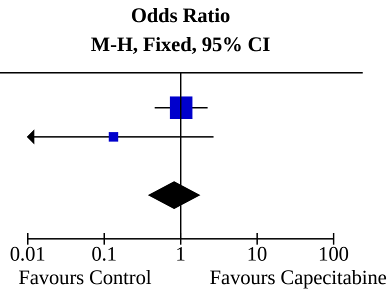
Odds Ratio
M-H, Fixed, 95% CI



Analysis 1.18. Comparison 1: Metastatic all: capecitabine-containing regimen vs non-capecitabine-containing regimen, Outcome 18: Complete response rate HR-

Study or Subgroup	Capecitabine Events	Capecitabine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
CHAT	15	62	17	71	78.1%	1.01 [0.46 , 2.25]
Fan 2013	0	26	3	27	21.9%	0.13 [0.01 , 2.69]
Total (95% CI)		**88**		**98**	**100.0%**	**0.82 [0.39 , 1.73]**
Total events:	15		20			

Heterogeneity: Chi² = 1.68, df = 1 (P = 0.19); I² = 41%
Test for overall effect: Z = 0.52 (P = 0.60)
Test for subgroup differences: Not applicable



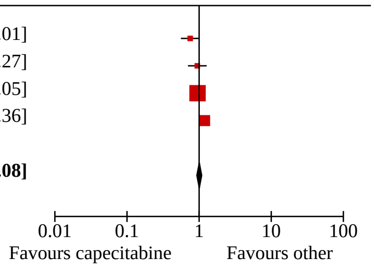
Comparison 2. Metastatic: capecitabine monotherapy vs chemotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 OS all	4	1783	Hazard Ratio (IV, Fixed, 95% CI)	1.00 [0.93, 1.08]
2.2 OS HR+	3	825	Hazard Ratio (IV, Fixed, 95% CI)	1.00 [0.86, 1.17]
2.3 OS HR-	3	803	Hazard Ratio (IV, Fixed, 95% CI)	1.09 [0.91, 1.29]
2.4 OS triple-negative	2	611	Hazard Ratio (IV, Fixed, 95% CI)	1.19 [0.98, 1.45]
2.5 PFS all	4	1783	Hazard Ratio (IV, Fixed, 95% CI)	0.92 [0.82, 1.04]
2.6 PFS HR+	3	825	Hazard Ratio (IV, Fixed, 95% CI)	0.84 [0.72, 0.99]
2.7 PFS HR-	3	803	Hazard Ratio (IV, Fixed, 95% CI)	1.01 [0.84, 1.21]
2.8 PFS triple-negative	2		Hazard Ratio (IV, Fixed, 95% CI)	1.16 [0.94, 1.41]
2.9 ORR all	4	1735	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.74, 1.26]
2.10 CBR all	2	1308	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.78, 1.26]
2.11 Complete response rate all	3	1456	Odds Ratio (M-H, Fixed, 95% CI)	2.04 [0.51, 8.20]

Analysis 2.1. Comparison 2: Metastatic: capecitabine monotherapy vs chemotherapy, Outcome 1: OS all

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
BOLERO6 (1)	-0.2852	0.1515	102	104	6.4%	0.75 [0.56 , 1.01]	
METRIC (1)	-0.0583	0.1528	109	218	6.3%	0.94 [0.70 , 1.27]	
Pallis 2012 (2)	-0.0511	0.0513	74	74	55.7%	0.95 [0.86 , 1.05]	
Study 301 (3)	0.1744	0.0681	548	554	31.6%	1.19 [1.04 , 1.36]	
Total (95% CI)			**833**	**950**	**100.0%**	**1.00 [0.93 , 1.08]**	

Heterogeneity: Chi² = 11.22, df = 3 (P = 0.01); I² = 73%
Test for overall effect: Z = 0.13 (P = 0.90)
Test for subgroup differences: Not applicable

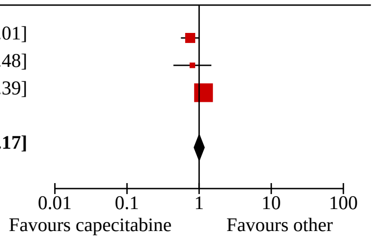


Footnotes
(1) HR inverted from published data
(2) Pallis - HR inverted from published data
(3) Results from pooled analysis (Pivot 2016) as EMBRACE did not report OS by capecitabine arm. HR inverted from published data.

Analysis 2.2. Comparison 2: Metastatic: capecitabine monotherapy vs chemotherapy, Outcome 2: OS HR+

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
BOLERO6 (1)	-0.2852	0.1515	102	104	27.0%	0.75 [0.56 , 1.01]	
Pallis 2012	-0.2152	0.3091	44	38	6.5%	0.81 [0.44 , 1.48]	
Study 301 (1)	0.1404	0.0965	278	259	66.5%	1.15 [0.95 , 1.39]	
Total (95% CI)			**424**	**401**	**100.0%**	**1.00 [0.86 , 1.17]**	

Heterogeneity: Chi² = 6.14, df = 2 (P = 0.05); I² = 67%
Test for overall effect: Z = 0.03 (P = 0.97)
Test for subgroup differences: Not applicable

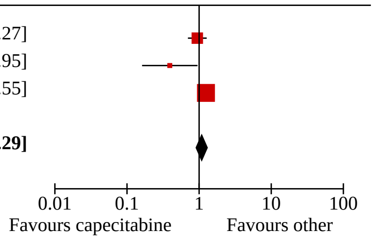


Footnotes
(1) HR inverted from published data

Analysis 2.3. Comparison 2: Metastatic: capecitabine monotherapy vs chemotherapy, Outcome 3: OS HR-

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
METRIC (1)	-0.0583	0.1528	109	218	33.3%	0.94 [0.70 , 1.27]	
Pallis 2012	-0.9365	0.4516	10	17	3.8%	0.39 [0.16 , 0.95]	
Study 301 (1)	0.2182	0.1113	216	233	62.8%	1.24 [1.00 , 1.55]	
Total (95% CI)			**335**	**468**	**100.0%**	**1.09 [0.91 , 1.29]**	

Heterogeneity: Chi² = 7.43, df = 2 (P = 0.02); I² = 73%
Test for overall effect: Z = 0.93 (P = 0.35)
Test for subgroup differences: Not applicable

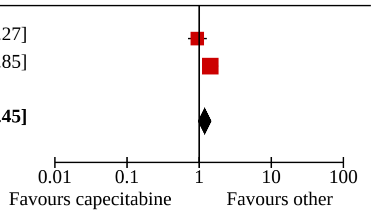


Footnotes
(1) HR inverted from published data

Analysis 2.4. Comparison 2: Metastatic: capecitabine monotherapy vs chemotherapy, Outcome 4: OS triple-negative

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
METRIC (1)	-0.0583	0.1528	109	218	42.9%	0.94 [0.70 , 1.27]	
Study 301 (1)	0.3538	0.1324	134	150	57.1%	1.42 [1.10 , 1.85]	
Total (95% CI)			**243**	**368**	**100.0%**	**1.19 [0.98 , 1.45]**	

Heterogeneity: Chi² = 4.15, df = 1 (P = 0.04); I² = 76%
Test for overall effect: Z = 1.77 (P = 0.08)
Test for subgroup differences: Not applicable

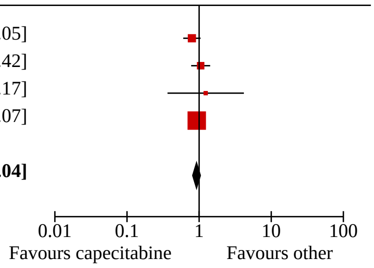


Footnotes
(1) HR inverted from published data

Analysis 2.5. Comparison 2: Metastatic: capecitabine monotherapy vs chemotherapy, Outcome 5: PFS all

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
BOLERO6 (1)	-0.2311	0.1407	102	104	18.6%	0.79 [0.60 , 1.05]	
METRIC	0.0488	0.1548	109	218	15.3%	1.05 [0.78 , 1.42]	
Pallis 2012	0.2097	0.622	74	74	0.9%	1.23 [0.36 , 4.17]	
Study 301 (1)	-0.076	0.0751	548	554	65.2%	0.93 [0.80 , 1.07]	
Total (95% CI)			**833**	**950**	**100.0%**	**0.92 [0.82 , 1.04]**	

Heterogeneity: Chi² = 2.06, df = 3 (P = 0.56); I² = 0%
Test for overall effect: Z = 1.37 (P = 0.17)
Test for subgroup differences: Not applicable

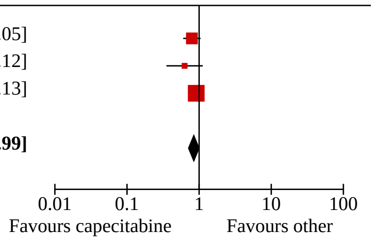


Footnotes
(1) HR inverted from published data

Analysis 2.6. Comparison 2: Metastatic: capecitabine monotherapy vs chemotherapy, Outcome 6: PFS HR+

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
BOLERO6 (1)	-0.2311	0.1407	102	104	34.8%	0.79 [0.60 , 1.05]	
Pallis 2012	-0.4638	0.2959	44	38	7.9%	0.63 [0.35 , 1.12]	
Study 301 (1)	-0.0926	0.1096	278	259	57.3%	0.91 [0.74 , 1.13]	
Total (95% CI)			**424**	**401**	**100.0%**	**0.84 [0.72 , 0.99]**	

Heterogeneity: Chi² = 1.67, df = 2 (P = 0.43); I² = 0%
Test for overall effect: Z = 2.05 (P = 0.04)
Test for subgroup differences: Not applicable

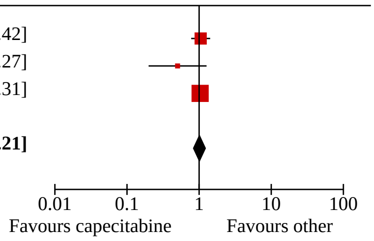


Footnotes
(1) HR inverted from published data

Analysis 2.7. Comparison 2: Metastatic: capecitabine monotherapy vs chemotherapy, Outcome 7: PFS HR-

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI
METRIC	0.0488	0.1548	109	218	36.7%	1.05 [0.78 , 1.42]
Pallis 2012	-0.6882	0.4721	10	17	3.9%	0.50 [0.20 , 1.27]
Study 301 (1)	0.0315	0.1217	216	233	59.4%	1.03 [0.81 , 1.31]
Total (95% CI)			**335**	**468**	**100.0%**	**1.01 [0.84 , 1.21]**

Heterogeneity: Chi² = 2.28, df = 2 (P = 0.32); I² = 12%
Test for overall effect: Z = 0.10 (P = 0.92)
Test for subgroup differences: Not applicable

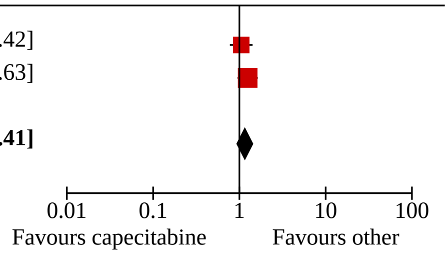


Footnotes
(1) HR inverted from published data

Analysis 2.8. Comparison 2: Metastatic: capecitabine monotherapy vs chemotherapy, Outcome 8: PFS triple-negative

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
METRIC	0.0488	0.1548	44.1%	1.05 [0.78 , 1.42]
Study 301 (1)	0.2206	0.1375	55.9%	1.25 [0.95 , 1.63]
Total (95% CI)			**100.0%**	**1.16 [0.94 , 1.41]**

Heterogeneity: Chi² = 0.69, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 1.41 (P = 0.16)
Test for subgroup differences: Not applicable

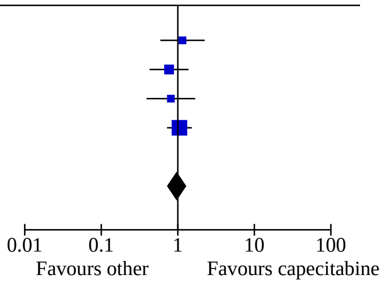


Footnotes
(1) HR inverted from published data

Analysis 2.9. Comparison 2: Metastatic: capecitabine monotherapy vs chemotherapy, Outcome 9: ORR all

Study or Subgroup	Capecitabine Events	Capecitabine Total	Other Events	Other Total	Weight	Odds Ratio M-H, Fixed, 95% CI
BOLERO6	23	102	21	104	14.4%	1.15 [0.59 , 2.24]
METRIC	21	100	46	179	23.3%	0.77 [0.43 , 1.38]
Pallis 2012	18	74	21	74	14.2%	0.81 [0.39 , 1.69]
Study 301	63	548	61	554	48.1%	1.05 [0.72 , 1.53]
Total (95% CI)		**824**		**911**	**100.0%**	**0.96 [0.74 , 1.26]**
Total events:	125		149			

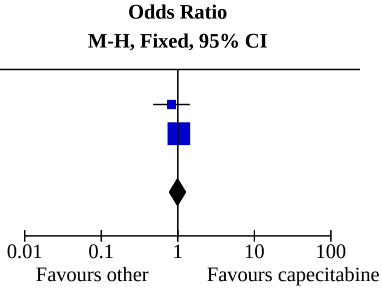
Heterogeneity: Chi² = 1.26, df = 3 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.79)
Test for subgroup differences: Not applicable



Analysis 2.10. Comparison 2: Metastatic: capecitabine monotherapy vs chemotherapy, Outcome 10: CBR all

Study or Subgroup	Capecitabine Events	Capecitabine Total	Other Events	Other Total	Weight	Odds Ratio M-H, Fixed, 95% CI
BOLERO6	53	102	59	104	21.0%	0.82 [0.48 , 1.43]
Study 301	147	548	145	554	79.0%	1.03 [0.79 , 1.35]
Total (95% CI)		**650**		**658**	**100.0%**	**0.99 [0.78 , 1.26]**
Total events:	200		204			

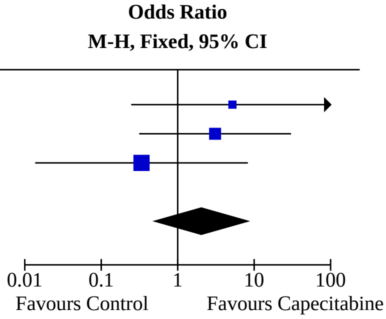
Heterogeneity: Chi² = 0.53, df = 1 (P = 0.47); I² = 0%
Test for overall effect: Z = 0.08 (P = 0.94)
Test for subgroup differences: Not applicable



Analysis 2.11. Comparison 2: Metastatic: capecitabine monotherapy vs chemotherapy, Outcome 11: Complete response rate all

Study or Subgroup	Capecitabine Events	Capecitabine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
BOLERO6	2	102	0	104	16.5%	5.20 [0.25 , 109.63]
Pallis 2012	3	74	1	74	32.7%	3.08 [0.31 , 30.36]
Study 301	0	548	1	554	50.8%	0.34 [0.01 , 8.28]
Total (95% CI)		**724**		**732**	**100.0%**	**2.04 [0.51 , 8.20]**
Total events:	5		2			

Heterogeneity: Chi² = 1.70, df = 2 (P = 0.43); I² = 0%
Test for overall effect: Z = 1.00 (P = 0.32)
Test for subgroup differences: Not applicable



Comparison 3. Metastatic: addition of capecitabine vs chemotherapy/other

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 OS all	4	1145	Hazard Ratio (IV, Fixed, 95% CI)	0.78 [0.66, 0.92]
3.2 OS HR+	2	324	Hazard Ratio (IV, Fixed, 95% CI)	0.62 [0.47, 0.81]
3.3 OS HR-	2	217	Hazard Ratio (IV, Fixed, 95% CI)	0.79 [0.59, 1.06]
3.4 OS triple-negative	1	46	Hazard Ratio (IV, Fixed, 95% CI)	0.44 [0.19, 1.02]
3.5 PFS all	4	1145	Hazard Ratio (IV, Fixed, 95% CI)	0.69 [0.60, 0.78]
3.6 PFS HR+	3	500	Hazard Ratio (IV, Fixed, 95% CI)	0.67 [0.55, 0.82]
3.7 PFS HR-	2	97	Hazard Ratio (IV, Fixed, 95% CI)	0.60 [0.39, 0.93]
3.8 PFS triple-negative	1	46	Hazard Ratio (IV, Fixed, 95% CI)	0.57 [0.31, 1.05]
3.9 ORR all	4	1145	Odds Ratio (M-H, Fixed, 95% CI)	1.37 [1.07, 1.75]
3.10 CBR all	1	185	Odds Ratio (M-H, Fixed, 95% CI)	1.96 [0.17, 21.96]

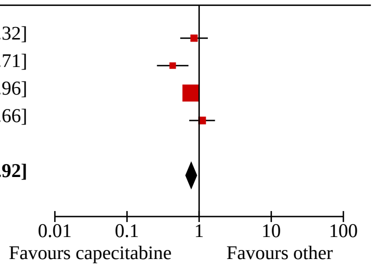
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.11 Complete response rate all	2	733	Odds Ratio (M-H, Fixed, 95% CI)	1.45 [0.86, 2.46]
3.12 Complete response rate HR+	1	89	Odds Ratio (M-H, Fixed, 95% CI)	4.62 [0.95, 22.51]
3.13 Complete response rate HR-	1	133	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.46, 2.25]

Analysis 3.1. Comparison 3: Metastatic: addition of capecitabine vs chemotherapy/other, Outcome 1: OS all

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CHAT	-0.1625	0.2246	112	110	14.2%	0.85 [0.55 , 1.32]
IMELDA	-0.844	0.2567	91	94	10.9%	0.43 [0.26 , 0.71]
SO140999	-0.2614	0.1105	255	256	58.7%	0.77 [0.62 , 0.96]
TABEA	0.0953	0.2099	111	116	16.3%	1.10 [0.73 , 1.66]
Total (95% CI)			**569**	**576**	**100.0%**	**0.78 [0.66 , 0.92]**

Heterogeneity: Chi² = 8.22, df = 3 (P = 0.04); I² = 64%
Test for overall effect: Z = 2.99 (P = 0.003)
Test for subgroup differences: Not applicable

Hazard Ratio IV, Fixed, 95% CI

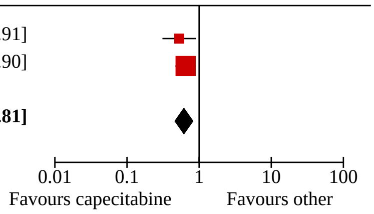


Analysis 3.2. Comparison 3: Metastatic: addition of capecitabine vs chemotherapy/other, Outcome 2: OS HR+

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI
IMELDA	-0.6349	0.2736	66	73	26.8%	0.53 [0.31 , 0.91]
SO140999	-0.4308	0.1654	90	95	73.2%	0.65 [0.47 , 0.90]
Total (95% CI)			**156**	**168**	**100.0%**	**0.62 [0.47 , 0.81]**

Heterogeneity: Chi² = 0.41, df = 1 (P = 0.52); I² = 0%
Test for overall effect: Z = 3.43 (P = 0.0006)
Test for subgroup differences: Not applicable

Hazard Ratio IV, Fixed, 95% CI

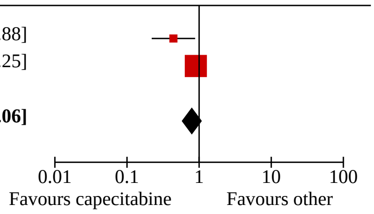


Analysis 3.3. Comparison 3: Metastatic: addition of capecitabine vs chemotherapy/other, Outcome 3: OS HR-

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI
IMELDA	-0.821	0.3537	25	21	18.1%	0.44 [0.22 , 0.88]
SO140999	-0.1054	0.166	88	83	81.9%	0.90 [0.65 , 1.25]
Total (95% CI)			**113**	**104**	**100.0%**	**0.79 [0.59 , 1.06]**

Heterogeneity: Chi² = 3.35, df = 1 (P = 0.07); I² = 70%
Test for overall effect: Z = 1.56 (P = 0.12)
Test for subgroup differences: Not applicable

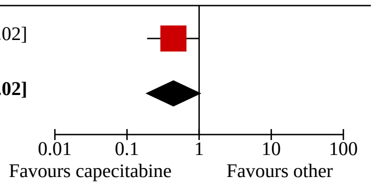
Hazard Ratio IV, Fixed, 95% CI



Analysis 3.4. Comparison 3: Metastatic: addition of capecitabine vs chemotherapy/other, Outcome 4: OS triple-negative

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI
IMELDA	-0.821	0.4285	25	21	100.0%	0.44 [0.19 , 1.02]
Total (95% CI)			**25**	**21**	**100.0%**	**0.44 [0.19 , 1.02]**

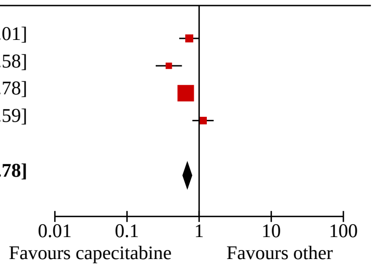
Heterogeneity: Not applicable
Test for overall effect: Z = 1.92 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3: Metastatic: addition of capecitabine vs chemotherapy/other, Outcome 5: PFS all

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CHAT	-0.3147	0.1634	112	110	17.7%	0.73 [0.53 , 1.01]
IMELDA	-0.9676	0.2136	91	94	10.3%	0.38 [0.25 , 0.58]
SO140999	-0.4277	0.0915	255	256	56.3%	0.65 [0.54 , 0.78]
TABEA	0.124	0.1733	111	116	15.7%	1.13 [0.81 , 1.59]
Total (95% CI)			**569**	**576**	**100.0%**	**0.69 [0.60 , 0.78]**

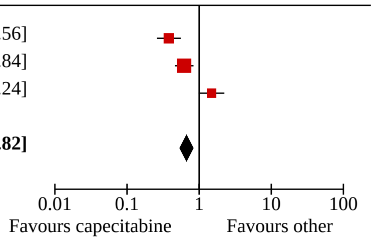
Heterogeneity: Chi² = 16.46, df = 3 (P = 0.0009); I² = 82%
Test for overall effect: Z = 5.49 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.6. Comparison 3: Metastatic: addition of capecitabine vs chemotherapy/other, Outcome 6: PFS HR+

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI
IMELDA	-0.9676	0.1936	66	73	28.8%	0.38 [0.26 , 0.56]
SO140999	-0.478	0.1523	90	95	46.5%	0.62 [0.46 , 0.84]
TABEA	0.3967	0.2091	86	90	24.7%	1.49 [0.99 , 2.24]
Total (95% CI)			**242**	**258**	**100.0%**	**0.67 [0.55 , 0.82]**

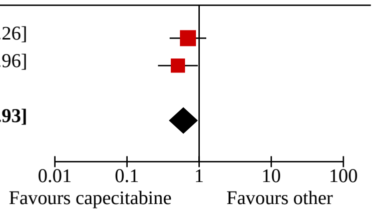
Heterogeneity: Chi² = 23.37, df = 2 (P < 0.00001); I² = 91%
Test for overall effect: Z = 3.88 (P = 0.0001)
Test for subgroup differences: Not applicable



Analysis 3.7. Comparison 3: Metastatic: addition of capecitabine vs chemotherapy/other, Outcome 7: PFS HR-

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI
IMELDA	-0.3567	0.2984	25	21	54.2%	0.70 [0.39 , 1.26]
TABEA	-0.6775	0.3243	25	26	45.8%	0.51 [0.27 , 0.96]
Total (95% CI)			**50**	**47**	**100.0%**	**0.60 [0.39 , 0.93]**

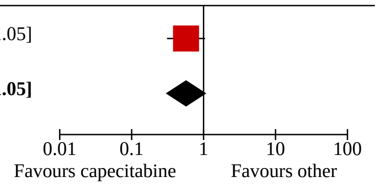
Heterogeneity: Chi² = 0.53, df = 1 (P = 0.47); I² = 0%
Test for overall effect: Z = 2.29 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 3.8. Comparison 3: Metastatic: addition of capecitabine vs chemotherapy/other, Outcome 8: PFS triple-negative

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI
IMELDA	-0.5621	0.3108	25	21	100.0%	0.57 [0.31 , 1.05]
Total (95% CI)			**25**	**21**	**100.0%**	**0.57 [0.31 , 1.05]**

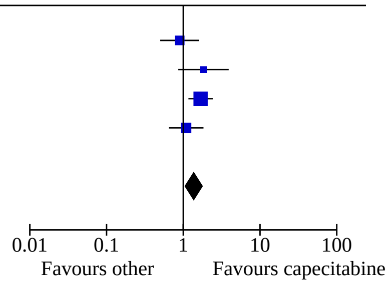
Heterogeneity: Not applicable
Test for overall effect: Z = 1.81 (P = 0.07)
Test for subgroup differences: Not applicable



Analysis 3.9. Comparison 3: Metastatic: addition of capecitabine vs chemotherapy/other, Outcome 9: ORR all

Study or Subgroup	Capecitabine Events	Capecitabine Total	Other Events	Other Total	Weight	Odds Ratio M-H, Fixed, 95% CI
CHAT	79	112	80	110	22.5%	0.90 [0.50 , 1.61]
IMELDA	78	91	72	94	9.6%	1.83 [0.86 , 3.91]
SO140999	107	255	77	256	42.2%	1.68 [1.17 , 2.42]
TABEA	55	111	55	116	25.7%	1.09 [0.65 , 1.83]
Total (95% CI)		**569**		**576**	**100.0%**	**1.37 [1.07 , 1.75]**
Total events:	319		284			

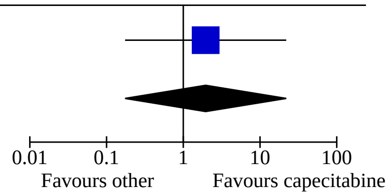
Heterogeneity: Chi² = 4.53, df = 3 (P = 0.21); I² = 34%
Test for overall effect: Z = 2.46 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 3.10. Comparison 3: Metastatic: addition of capecitabine vs chemotherapy/other, Outcome 10: CBR all

Study or Subgroup	Capecitabine Events	Capecitabine Total	Other Events	Other Total	Weight	Odds Ratio M-H, Fixed, 95% CI
IMELDA	90	91	92	94	100.0%	1.96 [0.17 , 21.96]
Total (95% CI)		**91**		**94**	**100.0%**	**1.96 [0.17 , 21.96]**
Total events:	90		92			

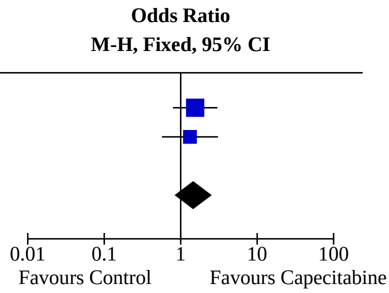
Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)
Test for subgroup differences: Not applicable



Analysis 3.11. Comparison 3: Metastatic: addition of capecitabine vs chemotherapy/other, Outcome 11: Complete response rate all

Study or Subgroup	Capecitabine Events	Capecitabine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
CHAT	26	112	18	110	59.6%	1.55 [0.79 , 3.02]
SO140999	13	255	10	256	40.4%	1.32 [0.57 , 3.07]
Total (95% CI)		**367**		**366**	**100.0%**	**1.45 [0.86 , 2.46]**
Total events:	39		28			

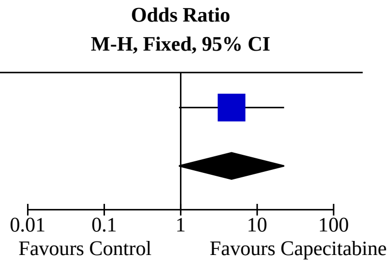
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² = 0%
Test for overall effect: Z = 1.40 (P = 0.16)
Test for subgroup differences: Not applicable



Analysis 3.12. Comparison 3: Metastatic: addition of capecitabine vs chemotherapy/other, Outcome 12: Complete response rate HR+

Study or Subgroup	Capecitabine Events	Capecitabine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
CHAT	10	50	2	39	100.0%	4.63 [0.95 , 22.51]
Total (95% CI)		**50**		**39**	**100.0%**	**4.63 [0.95 , 22.51]**
Total events:	10		2			

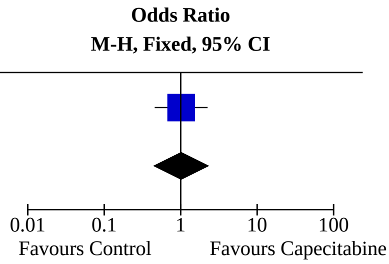
Heterogeneity: Not applicable
Test for overall effect: Z = 1.90 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 3.13. Comparison 3: Metastatic: addition of capecitabine vs chemotherapy/other, Outcome 13: Complete response rate HR-

Study or Subgroup	Capecitabine Events	Capecitabine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
CHAT	15	62	17	71	100.0%	1.01 [0.46 , 2.25]
Total (95% CI)		**62**		**71**	**100.0%**	**1.01 [0.46 , 2.25]**
Total events:	15		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.97)
Test for subgroup differences: Not applicable



Comparison 4. Metastatic: substitution of capecitabine vs chemotherapy/other

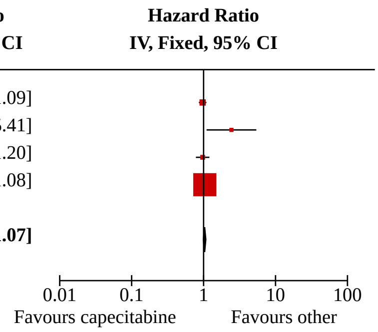
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 OS all	4	1397	Hazard Ratio (IV, Fixed, 95% CI)	1.03 [0.99, 1.07]
4.2 OS hormone receptor-positive	2	887	Hazard Ratio (IV, Fixed, 95% CI)	1.02 [0.84, 1.23]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.3 OS hormone receptor-negative	3	643	Hazard Ratio (IV, Fixed, 95% CI)	1.00 [0.79, 1.26]
4.4 OS triple-negative	2	183	Hazard Ratio (IV, Fixed, 95% CI)	1.59 [1.03, 2.43]
4.5 PFS all	4	1397	Hazard Ratio (IV, Fixed, 95% CI)	1.06 [0.93, 1.20]
4.6 PFS hormone receptor-positive	1	471	Hazard Ratio (IV, Fixed, 95% CI)	0.95 [0.78, 1.17]
4.7 PFS hormone receptor-negative	2	308	Hazard Ratio (IV, Fixed, 95% CI)	1.02 [0.79, 1.31]
4.8 PFS triple-negative	2	183	Hazard Ratio (IV, Fixed, 95% CI)	1.78 [1.28, 2.47]
4.9 ORR all	4	1320	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.58, 0.91]
4.10 ORR TNBC	2	183	Odds Ratio (M-H, Fixed, 95% CI)	0.20 [0.10, 0.39]
4.11 CBR all	1	53	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.10, 1.27]
4.12 Complete response rate all	1	53	Odds Ratio (M-H, Fixed, 95% CI)	0.13 [0.01, 2.69]

Analysis 4.1. Comparison 4: Metastatic: substitution of capecitabine vs chemotherapy/other, Outcome 1: OS all

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Chan 2009 (1)	-0.0305	0.0614	152	153	10.0%	0.97 [0.86 , 1.09]
Fan 2013	0.8916	0.4063	26	27	0.2%	2.44 [1.10 , 5.41]
Seidman 2011 (2)	-0.0305	0.1104	236	239	3.1%	0.97 [0.78 , 1.20]
TURANDOT	0.0392	0.0208	279	285	86.7%	1.04 [1.00 , 1.08]
Total (95% CI)			**693**	**704**	**100.0%**	**1.03 [0.99 , 1.07]**

Heterogeneity: Chi² = 5.95, df = 3 (P = 0.11); I² = 50%
Test for overall effect: Z = 1.65 (P = 0.10)
Test for subgroup differences: Not applicable



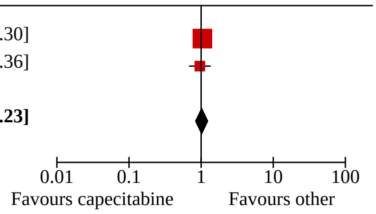
Footnotes
(1) HR calculated using Revman calculator
(2) HR inverted from reported data

Analysis 4.2. Comparison 4: Metastatic: substitution of capecitabine vs chemotherapy/other, Outcome 2: OS hormone receptor-positive

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Seidman 2011 (1)	0.0408	0.1139	238	233	70.5%	1.04 [0.83 , 1.30]
TURANDOT	-0.0408	0.1759	201	215	29.5%	0.96 [0.68 , 1.36]
Total (95% CI)			**439**	**448**	**100.0%**	**1.02 [0.84 , 1.23]**

Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 0.17 (P = 0.86)
Test for subgroup differences: Not applicable

Hazard Ratio
IV, Fixed, 95% CI



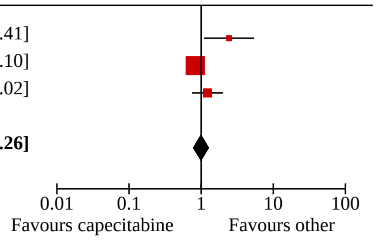
Footnotes
(1) Data from pooled analysis (Seidman 2014) as outcomes by hormone receptor status not reported in primary papers. HR inverted from published data.

Analysis 4.3. Comparison 4: Metastatic: substitution of capecitabine vs chemotherapy/other, Outcome 3: OS hormone receptor-negative

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Fan 2013	0.8916	0.4063	26	27	8.8%	2.44 [1.10 , 5.41]
Seidman 2011 (1)	-0.1906	0.1457	119	136	68.4%	0.83 [0.62 , 1.10]
TURANDOT	0.207	0.2524	168	167	22.8%	1.23 [0.75 , 2.02]
Total (95% CI)			**313**	**330**	**100.0%**	**1.00 [0.79 , 1.26]**

Heterogeneity: Chi² = 7.20, df = 2 (P = 0.03); I² = 72%
Test for overall effect: Z = 0.04 (P = 0.97)
Test for subgroup differences: Not applicable

Hazard Ratio
IV, Fixed, 95% CI



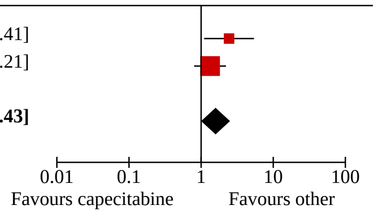
Footnotes
(1) Data from pooled analysis (Seidman 2014) as outcomes by hormone receptor status not reported in primary papers. HR inverted from published data.

Analysis 4.4. Comparison 4: Metastatic: substitution of capecitabine vs chemotherapy/other, Outcome 4: OS triple-negative

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Fan 2013	0.8916	0.4063	26	27	29.0%	2.44 [1.10 , 5.41]
TURANDOT	0.2852	0.2594	67	63	71.0%	1.33 [0.80 , 2.21]
Total (95% CI)			**93**	**90**	**100.0%**	**1.59 [1.03 , 2.43]**

Heterogeneity: Chi² = 1.58, df = 1 (P = 0.21); I² = 37%
Test for overall effect: Z = 2.11 (P = 0.04)
Test for subgroup differences: Not applicable

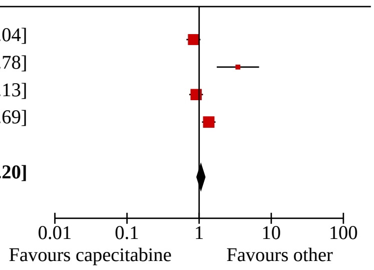
Hazard Ratio
IV, Fixed, 95% CI



Analysis 4.5. Comparison 4: Metastatic: substitution of capecitabine vs chemotherapy/other, Outcome 5: PFS all

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Chan 2009 (1)	-0.1823	0.1139	152	153	31.0%	0.83 [0.67 , 1.04]
Fan 2013	1.2379	0.3448	26	27	3.4%	3.45 [1.75 , 6.78]
Seidman 2011	-0.0962	0.1115	236	239	32.4%	0.91 [0.73 , 1.13]
TURANDOT	0.3075	0.11	279	285	33.2%	1.36 [1.10 , 1.69]
Total (95% CI)			**693**	**704**	**100.0%**	**1.06 [0.93 , 1.20]**

Heterogeneity: Chi² = 23.22, df = 3 (P < 0.0001); I² = 87%
Test for overall effect: Z = 0.89 (P = 0.37)
Test for subgroup differences: Not applicable

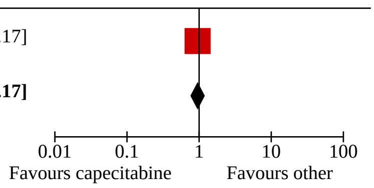


Footnotes
(1) HR inverted from published data.

Analysis 4.6. Comparison 4: Metastatic: substitution of capecitabine vs chemotherapy/other, Outcome 6: PFS hormone receptor-positive

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Seidman 2011 (1)	-0.0488	0.105	238	233	100.0%	0.95 [0.78 , 1.17]
Total (95% CI)			**238**	**233**	**100.0%**	**0.95 [0.78 , 1.17]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.64)
Test for subgroup differences: Not applicable

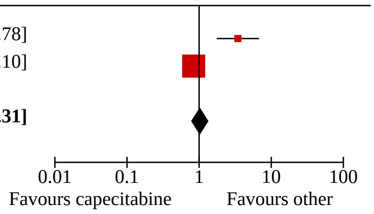


Footnotes
(1) Data from pooled analysis (Seidman 2014) as outcomes by hormone receptor status not reported in primary papers. HR inverted from reported data.

Analysis 4.7. Comparison 4: Metastatic: substitution of capecitabine vs chemotherapy/other, Outcome 7: PFS hormone receptor-negative

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Fan 2013	1.2379	0.3448	26	27	13.8%	3.45 [1.75 , 6.78]
Seidman 2011 (1)	-0.174	0.1381	119	136	86.2%	0.84 [0.64 , 1.10]
Total (95% CI)			**145**	**163**	**100.0%**	**1.02 [0.79 , 1.31]**

Heterogeneity: Chi² = 14.45, df = 1 (P = 0.0001); I² = 93%
Test for overall effect: Z = 0.17 (P = 0.87)
Test for subgroup differences: Not applicable

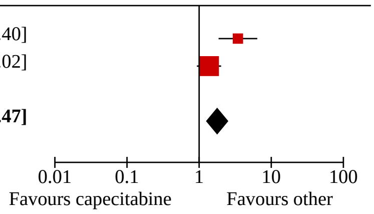


Footnotes
(1) Data from pooled analysis (Seidman 2014) as outcomes by hormone receptor status not reported in primary papers. HR inverted from reported data.

Analysis 4.8. Comparison 4: Metastatic: substitution of capecitabine vs chemotherapy/other, Outcome 8: PFS triple-negative

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Fan 2013	1.2384	0.3152	26	27	28.2%	3.45 [1.86 , 6.40]
TURANDOT	0.3148	0.1976	67	63	71.8%	1.37 [0.93 , 2.02]
Total (95% CI)			**93**	**90**	**100.0%**	**1.78 [1.28 , 2.47]**

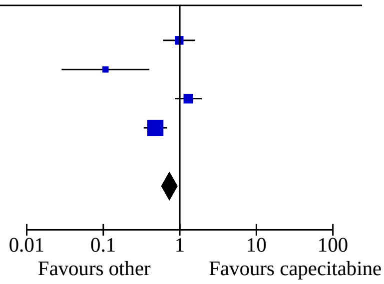
Heterogeneity: Chi² = 6.16, df = 1 (P = 0.01); I² = 84%
Test for overall effect: Z = 3.44 (P = 0.0006)
Test for subgroup differences: Not applicable



Analysis 4.9. Comparison 4: Metastatic: substitution of capecitabine vs chemotherapy/other, Outcome 9: ORR all

Study or Subgroup	Capecitabine Events	Capecitabine Total	Other Events	Other Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Chan 2009	48	152	49	153	18.7%	0.98 [0.60 , 1.59]
Fan 2013	4	26	17	27	7.9%	0.11 [0.03 , 0.40]
Seidman 2011	78	191	72	207	22.9%	1.29 [0.86 , 1.94]
TURANDOT	76	279	125	285	50.4%	0.48 [0.34 , 0.68]
Total (95% CI)		**648**		**672**	**100.0%**	**0.73 [0.58 , 0.91]**
Total events:	206		263			

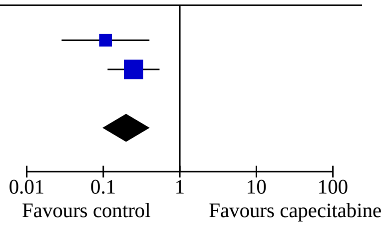
Heterogeneity: Chi² = 22.66, df = 3 (P < 0.0001); I² = 87%
Test for overall effect: Z = 2.74 (P = 0.006)
Test for subgroup differences: Not applicable



Analysis 4.10. Comparison 4: Metastatic: substitution of capecitabine vs chemotherapy/other, Outcome 10: ORR TNBC

Study or Subgroup	Capecitabine Events	Capecitabine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Fan 2013	4	26	17	27	35.4%	0.11 [0.03 , 0.40]
TURANDOT	13	67	31	63	64.6%	0.25 [0.11 , 0.54]
Total (95% CI)		**93**		**90**	**100.0%**	**0.20 [0.10 , 0.39]**
Total events:	17		48			

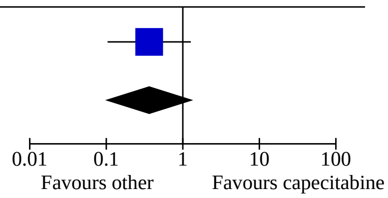
Heterogeneity: Chi² = 1.16, df = 1 (P = 0.28); I² = 14%
Test for overall effect: Z = 4.75 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 4.11. Comparison 4: Metastatic: substitution of capecitabine vs chemotherapy/other, Outcome 11: CBR all

Study or Subgroup	Capecitabine Events	Capecitabine Total	Other Events	Other Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Fan 2013	16	26	22	27	100.0%	0.36 [0.10 , 1.27]
Total (95% CI)		**26**		**27**	**100.0%**	**0.36 [0.10 , 1.27]**
Total events:	16		22			

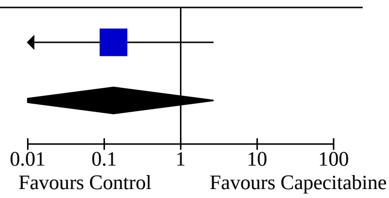
Heterogeneity: Not applicable
Test for overall effect: Z = 1.58 (P = 0.11)
Test for subgroup differences: Not applicable



Analysis 4.12. Comparison 4: Metastatic: substitution of capecitabine vs chemotherapy/other, Outcome 12: Complete response rate all

Study or Subgroup	Capecitabine Events	Capecitabine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Fan 2013	0	26	3	27	100.0%	0.13 [0.01 , 2.69]
Total (95% CI)		**26**		**27**	**100.0%**	**0.13 [0.01 , 2.69]**
Total events:	0		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.32 (P = 0.19)
Test for subgroup differences: Not applicable



Comparison 5. Adjuvant all: capecitabine-containing regimen vs other regimen

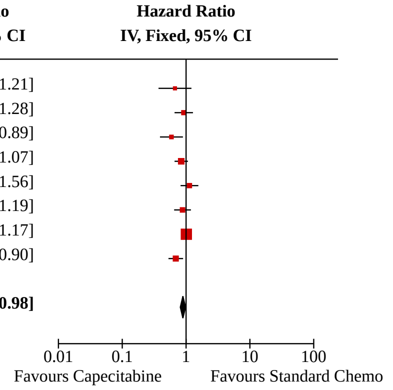
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 OS (all)	8	13547	Hazard Ratio (IV, Fixed, 95% CI)	0.89 [0.81, 0.98]
5.2 OS hormone receptor-positive	3	3683	Hazard Ratio (IV, Fixed, 95% CI)	0.86 [0.68, 1.09]
5.3 OS hormone receptor-negative	5	3432	Hazard Ratio (IV, Fixed, 95% CI)	0.72 [0.59, 0.89]
5.4 OS triple-negative	5	3306	Hazard Ratio (IV, Fixed, 95% CI)	0.70 [0.57, 0.86]
5.5 AE - Anaemia	4	6425	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.33, 0.84]
5.6 AE - Neutropenia	7	9849	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.74, 0.90]
5.7 AE - Febrile neutropenia	5	8086	Odds Ratio (M-H, Fixed, 95% CI)	0.55 [0.47, 0.64]
5.8 AE - Thrombocytopenia	5	5883	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.57, 1.81]
5.9 AE - Hand-foot syndrome	8	11207	Odds Ratio (M-H, Fixed, 95% CI)	13.60 [10.65, 17.37]
5.10 AE - Mucositis	6	8988	Odds Ratio (M-H, Fixed, 95% CI)	1.27 [1.03, 1.56]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.11 AE - Diarrhoea	8	11207	Odds Ratio (M-H, Fixed, 95% CI)	2.46 [2.01, 3.01]
5.12 AE - Ischaemic heart disease	3	3724	Odds Ratio (M-H, Fixed, 95% CI)	3.39 [0.70, 16.37]
5.13 AE - Treatment-related death	5	8427	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.21, 1.33]

Analysis 5.1. Comparison 5: Adjuvant all: capecitabine-containing regimen vs other regimen, Outcome 1: OS (all)

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Standard Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CBCSG-10	-0.4005	0.303	273	288	2.5%	0.67 [0.37 , 1.21]
CIBOMA 2004-01	-0.0834	0.1695	448	428	7.9%	0.92 [0.66 , 1.28]
CREATE-X	-0.5276	0.2112	430	436	5.1%	0.59 [0.39 , 0.89]
FINXX	-0.1744	0.123	753	747	15.0%	0.84 [0.66 , 1.07]
GEICAM 2003-10	0.1222	0.1636	715	669	8.5%	1.13 [0.82 , 1.56]
ICE (1)	-0.1278	0.1546	681	677	9.5%	0.88 [0.65 , 1.19]
TACT2	0.01	0.0761	2189	2202	39.1%	1.01 [0.87 , 1.17]
USON 01062	-0.3711	0.1346	1307	1304	12.5%	0.69 [0.53 , 0.90]
Total (95% CI)			**6796**	**6751**	**100.0%**	**0.89 [0.81 , 0.98]**

Heterogeneity: Chi² = 13.40, df = 7 (P = 0.06); I² = 48%
Test for overall effect: Z = 2.39 (P = 0.02)
Test for subgroup differences: Not applicable

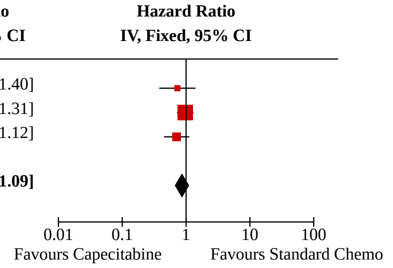


Footnotes
(1) ICE: HR inverted

Analysis 5.2. Comparison 5: Adjuvant all: capecitabine-containing regimen vs other regimen, Outcome 2: OS hormone receptor-positive

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Standard Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CREATE-X	-0.3147	0.3331	443	444	12.7%	0.73 [0.38 , 1.40]
FINXX (1)	-0.0305	0.1521	597	574	61.1%	0.97 [0.72 , 1.31]
USON 01062	-0.3425	0.2327	808	817	26.1%	0.71 [0.45 , 1.12]
Total (95% CI)			**1848**	**1835**	**100.0%**	**0.86 [0.68 , 1.09]**

Heterogeneity: Chi² = 1.55, df = 2 (P = 0.46); I² = 0%
Test for overall effect: Z = 1.25 (P = 0.21)
Test for subgroup differences: Not applicable

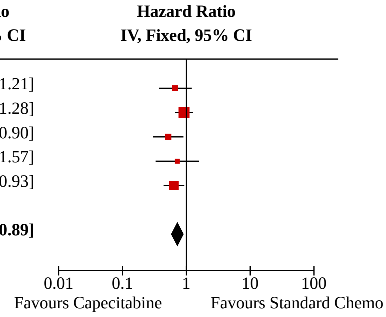


Footnotes
(1) FINXX - - calculated using REVMAN (combined hazard ratio of ER+/HER2+ and ER+/HER2-)

Analysis 5.3. Comparison 5: Adjuvant all: capecitabine-containing regimen vs other regimen, Outcome 3: OS hormone receptor-negative

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Standard Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CBCSG-10	-0.4005	0.303	273	288	11.8%	0.67 [0.37 , 1.21]
CIBOMA 2004-01	-0.0834	0.1695	448	428	37.8%	0.92 [0.66 , 1.28]
CREATE-X	-0.6539	0.2806	443	444	13.8%	0.52 [0.30 , 0.90]
FINXX	-0.3285	0.398	61	61	6.9%	0.72 [0.33 , 1.57]
USON 01062	-0.4463	0.1912	499	487	29.7%	0.64 [0.44 , 0.93]
Total (95% CI)			**1724**	**1708**	**100.0%**	**0.72 [0.59 , 0.89]**

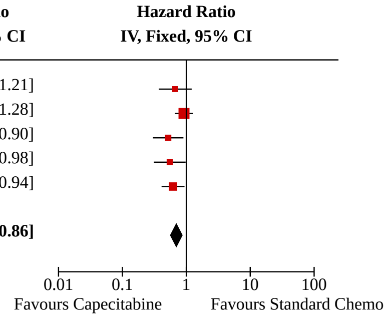
Heterogeneity: Chi² = 3.87, df = 4 (P = 0.42); I² = 0%
Test for overall effect: Z = 3.11 (P = 0.002)
Test for subgroup differences: Not applicable



Analysis 5.4. Comparison 5: Adjuvant all: capecitabine-containing regimen vs other regimen, Outcome 4: OS triple-negative

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Standard Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CBCSG-10	-0.4005	0.303	273	288	11.8%	0.67 [0.37 , 1.21]
CIBOMA 2004-01	-0.0834	0.1695	448	428	37.6%	0.92 [0.66 , 1.28]
CREATE-X	-0.6539	0.2806	443	444	13.7%	0.52 [0.30 , 0.90]
FINXX	-0.5978	0.2925	93	109	12.6%	0.55 [0.31 , 0.98]
USON 01062	-0.478	0.211	396	384	24.3%	0.62 [0.41 , 0.94]
Total (95% CI)			**1653**	**1653**	**100.0%**	**0.70 [0.57 , 0.86]**

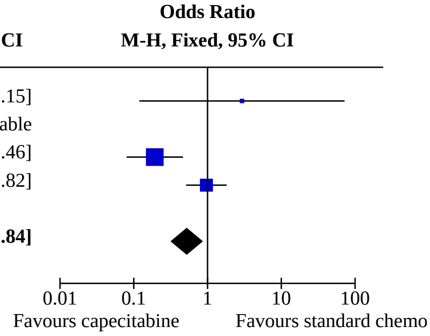
Heterogeneity: Chi² = 4.75, df = 4 (P = 0.31); I² = 16%
Test for overall effect: Z = 3.46 (P = 0.0005)
Test for subgroup differences: Not applicable



Analysis 5.5. Comparison 5: Adjuvant all: capecitabine-containing regimen vs other regimen, Outcome 5: AE - Anaemia

Study or Subgroup	Capecitabine Events	Capecitabine Total	Standard Chemo Events	Standard Chemo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
CIBOMA 2004-01	1	436	0	425	1.0%	2.93 [0.12 , 72.15]
CREATE-X	0	443	0	459		Not estimable
TACT2	6	1044	30	1030	60.0%	0.19 [0.08 , 0.46]
USON 01062	19	1283	20	1305	39.0%	0.97 [0.51 , 1.82]
Total (95% CI)		**3206**		**3219**	**100.0%**	**0.52 [0.33 , 0.84]**
Total events:	26		50			

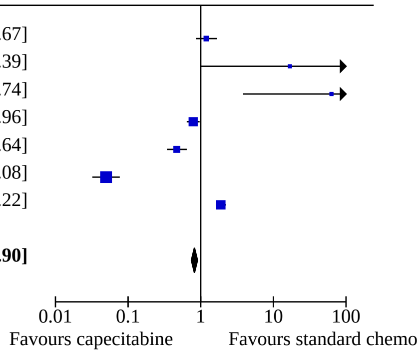
Heterogeneity: Chi² = 9.67, df = 2 (P = 0.008); I² = 79%
Test for overall effect: Z = 2.70 (P = 0.007)
Test for subgroup differences: Not applicable



Analysis 5.6. Comparison 5: Adjuvant all: capecitabine-containing regimen vs other regimen, Outcome 6: AE - Neutropenia

Study or Subgroup	Capecitabine Events	Capecitabine Total	Standard Chemo Events	Standard Chemo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
CBCSG-10	134	288	115	273	6.9%	1.20 [0.86 , 1.67]
CIBOMA 2004-01	8	436	0	425	0.1%	16.88 [0.97 , 293.39]
CREATE-X	28	443	0	459	0.0%	63.04 [3.84 , 1035.74]
FINXX	325	744	368	741	22.6%	0.79 [0.64 , 0.96]
GEICAM 2003-10	70	711	126	667	12.7%	0.47 [0.34 , 0.64]
TACT2	23	1044	321	1030	34.4%	0.05 [0.03 , 0.08]
USON 01062	896	1283	718	1305	23.3%	1.89 [1.61 , 2.22]
Total (95% CI)		**4949**		**4900**	**100.0%**	**0.82 [0.74 , 0.90]**
Total events:	1484		1648			

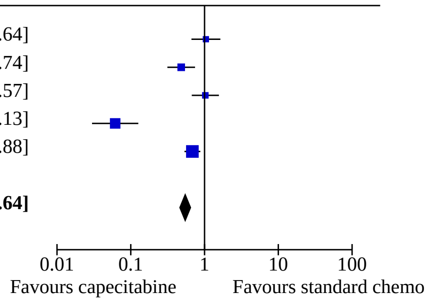
Heterogeneity: Chi² = 294.22, df = 6 (P < 0.00001); I² = 98%
Test for overall effect: Z = 4.07 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 5.7. Comparison 5: Adjuvant all: capecitabine-containing regimen vs other regimen, Outcome 7: AE - Febrile neutropenia

Study or Subgroup	Capecitabine Events	Capecitabine Total	Standard Chemo Events	Standard Chemo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
CBCSG-10	47	288	43	273	9.0%	1.04 [0.66 , 1.64]
FINXX	33	744	65	741	15.2%	0.48 [0.31 , 0.74]
GEICAM 2003-10	48	711	44	667	10.3%	1.03 [0.67 , 1.57]
TACT2	8	1044	115	1030	28.0%	0.06 [0.03 , 0.13]
USON 01062	120	1283	171	1305	37.5%	0.68 [0.53 , 0.88]
Total (95% CI)		**4070**		**4016**	**100.0%**	**0.55 [0.47 , 0.64]**
Total events:	256		438			

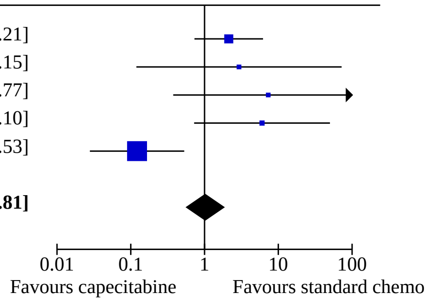
Heterogeneity: Chi² = 55.02, df = 4 (P < 0.00001); I² = 93%
Test for overall effect: Z = 7.32 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 5.8. Comparison 5: Adjuvant all: capecitabine-containing regimen vs other regimen, Outcome 8: AE - Thrombocytopenia

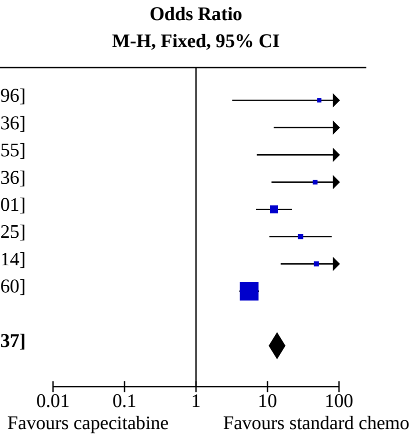
Study or Subgroup	Capecitabine Events	Capecitabine Total	Standard Chemo Events	Standard Chemo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
CBCSG-10	11	288	5	273	21.5%	2.13 [0.73 , 6.21]
CIBOMA 2004-01	1	436	0	425	2.2%	2.93 [0.12 , 72.15]
CREATE-X	3	443	0	459	2.1%	7.30 [0.38 , 141.77]
FINXX	6	744	1	741	4.3%	6.02 [0.72 , 50.10]
TACT2	2	1044	16	1030	69.9%	0.12 [0.03 , 0.53]
Total (95% CI)		**2955**		**2928**	**100.0%**	**1.02 [0.57 , 1.81]**
Total events:	23		22			

Heterogeneity: Chi² = 14.63, df = 4 (P = 0.006); I² = 73%
Test for overall effect: Z = 0.07 (P = 0.94)
Test for subgroup differences: Not applicable



Analysis 5.9. Comparison 5: Adjuvant all: capecitabine-containing regimen vs other regimen, Outcome 9: AE - Hand-foot syndrome

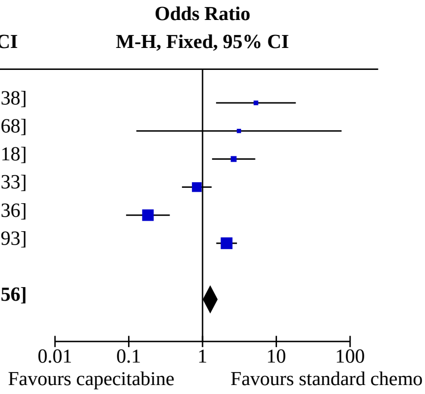
Study or Subgroup	Capecitabine Events	Capecitabine Total	Standard Chemo Events	Standard Chemo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
CBCSG-10	25	288	0	273	0.8%	52.94 [3.21 , 873.96]
CIBOMA 2004-01	82	436	0	425	0.7%	198.05 [12.24 , 3204.36]
CREATE-X	49	443	0	459	0.7%	115.31 [7.09 , 1875.55]
FINXX	83	744	2	741	2.9%	46.40 [11.37 , 189.36]
GEICAM 2003-10	140	711	13	667	17.8%	12.33 [6.91 , 22.01]
ICE	99	677	4	681	5.6%	28.99 [10.60 , 79.25]
TACT2	129	1044	3	1030	4.4%	48.26 [15.31 , 152.14]
USON 01062	232	1283	50	1305	67.1%	5.54 [4.04 , 7.60]
Total (95% CI)		**5626**		**5581**	**100.0%**	**13.60 [10.65 , 17.37]**
Total events:	839		72			



Heterogeneity: Chi² = 47.55, df = 7 (P < 0.00001); I² = 85%
Test for overall effect: Z = 20.93 (P < 0.00001)
Test for subgroup differences: Not applicable

Analysis 5.10. Comparison 5: Adjuvant all: capecitabine-containing regimen vs other regimen, Outcome 10: AE - Mucositis

Study or Subgroup	Capecitabine Events	Capecitabine Total	Standard Chemo Events	Standard Chemo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
CBCSG-10	16	288	3	273	1.8%	5.29 [1.53 , 18.38]
CREATE-X	1	443	0	459	0.3%	3.12 [0.13 , 76.68]
FINXX	31	744	12	741	7.2%	2.64 [1.35 , 5.18]
GEICAM 2003-10	36	711	40	667	24.6%	0.84 [0.53 , 1.33]
TACT2	10	1044	52	1030	32.6%	0.18 [0.09 , 0.36]
USON 01062	117	1283	59	1305	33.4%	2.12 [1.53 , 2.93]
Total (95% CI)		**4513**		**4475**	**100.0%**	**1.27 [1.03 , 1.56]**
Total events:	211		166			

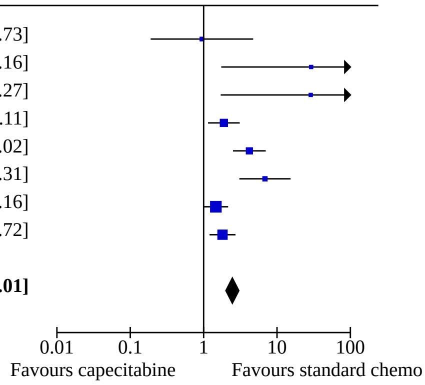


Heterogeneity: Chi² = 53.82, df = 5 (P < 0.00001); I² = 91%
Test for overall effect: Z = 2.26 (P = 0.02)
Test for subgroup differences: Not applicable

Analysis 5.11. Comparison 5: Adjuvant all: capecitabine-containing regimen vs other regimen, Outcome 11: AE - Diarrhoea

Study or Subgroup	Capecitabine Events	Capecitabine Total	Standard Chemo Events	Standard Chemo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
CBCSG-10	3	288	3	273	2.3%	0.95 [0.19 , 4.73]
CIBOMA 2004-01	14	436	0	425	0.4%	29.21 [1.74 , 491.16]
CREATE-X	13	443	0	459	0.4%	28.82 [1.71 , 486.27]
FINXX	46	744	25	741	18.0%	1.89 [1.15 , 3.11]
GEICAM 2003-10	78	711	19	667	13.4%	4.20 [2.52 , 7.02]
ICE	45	677	7	681	5.0%	6.86 [3.07 , 15.31]
TACT2	67	1044	46	1030	33.2%	1.47 [1.00 , 2.16]
USON 01062	66	1283	38	1305	27.4%	1.81 [1.20 , 2.72]
Total (95% CI)		**5626**		**5581**	**100.0%**	**2.46 [2.01 , 3.01]**
Total events:	332		138			

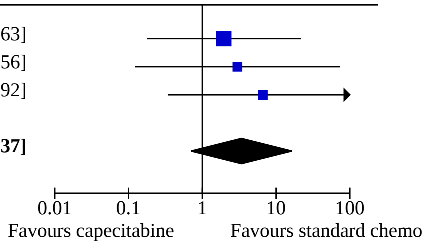
Heterogeneity: Chi² = 27.86, df = 7 (P = 0.0002); I² = 75%
Test for overall effect: Z = 8.74 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 5.12. Comparison 5: Adjuvant all: capecitabine-containing regimen vs other regimen, Outcome 12: AE - Ischaemic heart disease

Study or Subgroup	Capecitabine Events	Capecitabine Total	Standard Chemo Events	Standard Chemo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
CIBOMA 2004-01	2	436	1	425	49.9%	1.95 [0.18 , 21.63]
FINXX	1	744	0	741	24.7%	2.99 [0.12 , 73.56]
GEICAM 2003-10	3	711	0	667	25.4%	6.59 [0.34 , 127.92]
Total (95% CI)		**1891**		**1833**	**100.0%**	**3.39 [0.70 , 16.37]**
Total events:	6		1			

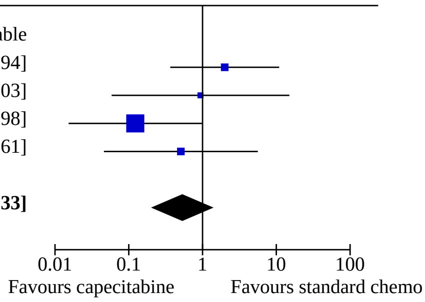
Heterogeneity: Chi² = 0.40, df = 2 (P = 0.82); I² = 0%
Test for overall effect: Z = 1.52 (P = 0.13)
Test for subgroup differences: Not applicable



Analysis 5.13. Comparison 5: Adjuvant all: capecitabine-containing regimen vs other regimen, Outcome 13: AE - Treatment-related death

Study or Subgroup	Capecitabine Events	Capecitabine Total	Standard Chemo Events	Standard Chemo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
CREATE-X	0	443	0	459		Not estimable
FINXX	4	744	2	741	15.3%	2.00 [0.36 , 10.94]
GEICAM 2003-10	1	711	1	667	7.9%	0.94 [0.06 , 15.03]
TACT2	1	1044	8	1030	61.7%	0.12 [0.02 , 0.98]
USON 01062	1	1283	2	1305	15.2%	0.51 [0.05 , 5.61]
Total (95% CI)		**4225**		**4202**	**100.0%**	**0.53 [0.21 , 1.33]**
Total events:	7		13			

Heterogeneity: Chi² = 4.40, df = 3 (P = 0.22); I² = 32%
Test for overall effect: Z = 1.35 (P = 0.18)
Test for subgroup differences: Not applicable

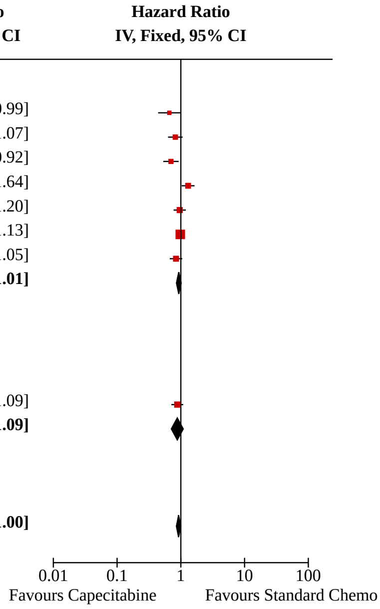


Comparison 6. Adjuvant All: Sensitivity analysis of combining DFS and RFS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 DFS and RFS together	8	13547	Hazard Ratio (IV, Fixed, 95% CI)	0.92 [0.85, 1.00]
6.1.1 DFS	7	12047	Hazard Ratio (IV, Fixed, 95% CI)	0.93 [0.85, 1.01]
6.1.2 RFS	1	1500	Hazard Ratio (IV, Fixed, 95% CI)	0.88 [0.71, 1.09]
6.2 DFS and RFS: Hormone Receptor Positive	5	5604	Hazard Ratio (IV, Fixed, 95% CI)	1.03 [0.91, 1.17]
6.2.1 DFS	4	4433	Hazard Ratio (IV, Fixed, 95% CI)	1.05 [0.91, 1.21]
6.2.2 RFS	1	1171	Hazard Ratio (IV, Fixed, 95% CI)	0.99 [0.78, 1.26]
6.3 DFS and RFS: Hormone Receptor Negative	7	3307	Hazard Ratio (IV, Fixed, 95% CI)	0.74 [0.64, 0.86]
6.3.1 DFS	6	3185	Hazard Ratio (IV, Fixed, 95% CI)	0.74 [0.64, 0.86]
6.3.2 RFS	1	122	Hazard Ratio (IV, Fixed, 95% CI)	0.82 [0.41, 1.64]
6.4 DFS and RFS: Triple negative	7	4339	Hazard Ratio (IV, Fixed, 95% CI)	0.83 [0.72, 0.95]
6.4.1 DFS	6	4137	Hazard Ratio (IV, Fixed, 95% CI)	0.85 [0.74, 0.98]
6.4.2 RFS	1	202	Hazard Ratio (IV, Fixed, 95% CI)	0.53 [0.31, 0.91]

Analysis 6.1. Comparison 6: Adjuvant All: Sensitivity analysis of combining DFS and RFS, Outcome 1: DFS and RFS together

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Standard Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
6.1.1 DFS						
CBCSG-10	-0.4155	0.2069	273	288	3.7%	0.66 [0.44 , 0.99]
CIBOMA 2004-01	-0.1985	0.1345	448	428	8.8%	0.82 [0.63 , 1.07]
CREATE-X	-0.3567	0.1419	430	436	7.9%	0.70 [0.53 , 0.92]
GEICAM 2003-10	0.2624	0.1188	715	669	11.3%	1.30 [1.03 , 1.64]
ICE (1)	-0.0408	0.1125	681	677	12.6%	0.96 [0.77 , 1.20]
TACT2 (2)	-0.0202	0.0726	2189	2202	30.3%	0.98 [0.85 , 1.13]
USON 01062	-0.1744	0.1154	1307	1304	12.0%	0.84 [0.67 , 1.05]
Subtotal (95% CI)			**6043**	**6004**	**86.7%**	**0.93 [0.85 , 1.01]**
Heterogeneity: Chi² = 16.96, df = 6 (P = 0.009); I² = 65%						
Test for overall effect: Z = 1.71 (P = 0.09)						
6.1.2 RFS						
FINXX	-0.1278	0.1095	753	747	13.3%	0.88 [0.71 , 1.09]
Subtotal (95% CI)			**753**	**747**	**13.3%**	**0.88 [0.71 , 1.09]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.17 (P = 0.24)						
Total (95% CI)			**6796**	**6751**	**100.0%**	**0.92 [0.85 , 1.00]**
Heterogeneity: Chi² = 17.17, df = 7 (P = 0.02); I² = 59%						
Test for overall effect: Z = 2.02 (P = 0.04)						
Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.64), I² = 0%						



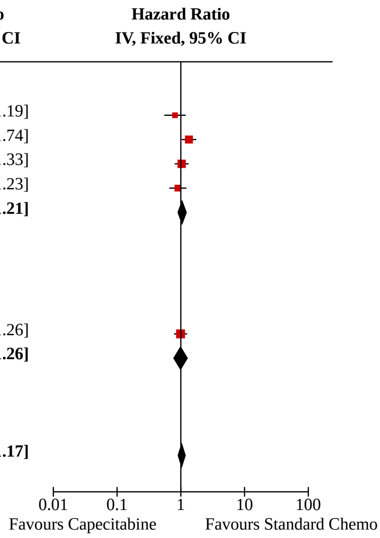
Footnotes

(1) ICE 5yr: HR 1.04 (95CI 0.84-1.29) - hazard ratio inverted for forest plot

(2) TACT2 5yr: presented as TTF HR 0.98 (0.85-1.14)

Analysis 6.2. Comparison 6: Adjuvant All: Sensitivity analysis of combining DFS and RFS, Outcome 2: DFS and RFS: Hormone Receptor Positive

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Standard Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
6.2.1 DFS						
CREATE-X	-0.2107	0.1975	275	275	10.3%	0.81 [0.55 , 1.19]
GEICAM 2003-10 (1)	0.2927	0.1342	594	565	22.3%	1.34 [1.03 , 1.74]
ICE	0.0296	0.1289	551	548	24.2%	1.03 [0.80 , 1.33]
USON 01062	-0.1054	0.1582	808	817	16.1%	0.90 [0.66 , 1.23]
Subtotal (95% CI)			**2228**	**2205**	**72.8%**	**1.05 [0.91 , 1.21]**
Heterogeneity: Chi² = 6.00, df = 3 (P = 0.11); I² = 50%						
Test for overall effect: Z = 0.63 (P = 0.53)						
6.2.2 RFS						
FINXX	-0.0101	0.1216	597	574	27.2%	0.99 [0.78 , 1.26]
Subtotal (95% CI)			**597**	**574**	**27.2%**	**0.99 [0.78 , 1.26]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.08 (P = 0.93)						
Total (95% CI)			**2825**	**2779**	**100.0%**	**1.03 [0.91 , 1.17]**
Heterogeneity: Chi² = 6.16, df = 4 (P = 0.19); I² = 35%						
Test for overall effect: Z = 0.49 (P = 0.62)						
Test for subgroup differences: Chi² = 0.16, df = 1 (P = 0.69), I² = 0%						

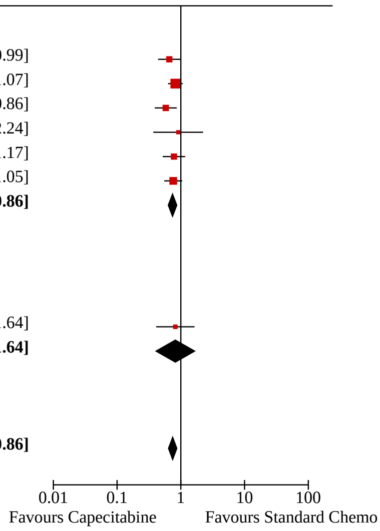


Footnotes

(1) GEICAM/200310 - calculated using REVMAN (combined hazard ratio of ER+/HER2+ and ER+/HER2-)

Analysis 6.3. Comparison 6: Adjuvant All: Sensitivity analysis of combining DFS and RFS, Outcome 3: DFS and RFS: Hormone Receptor Negative

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Standard Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
6.3.1 DFS						
CBCSG-10	-0.4155	0.2069	273	288	13.3%	0.66 [0.44 , 0.99]
CIBOMA 2004-01	-0.1985	0.1345	448	428	31.4%	0.82 [0.63 , 1.07]
CREATE-X	-0.5447	0.2025	141	143	13.9%	0.58 [0.39 , 0.86]
GEICAM 2003-10 (1)	-0.0943	0.4592	121	98	2.7%	0.91 [0.37 , 2.24]
ICE	-0.2485	0.2069	130	129	13.3%	0.78 [0.52 , 1.17]
USON 01062	-0.2744	0.165	499	487	20.9%	0.76 [0.55 , 1.05]
Subtotal (95% CI)			**1612**	**1573**	**95.5%**	**0.74 [0.64 , 0.86]**
Heterogeneity: Chi² = 2.63, df = 5 (P = 0.76); I² = 0%						
Test for overall effect: Z = 3.88 (P = 0.0001)						
6.3.2 RFS						
FINXX	-0.1985	0.3537	61	61	4.5%	0.82 [0.41 , 1.64]
Subtotal (95% CI)			**61**	**61**	**4.5%**	**0.82 [0.41 , 1.64]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.57)						
Total (95% CI)			**1673**	**1634**	**100.0%**	**0.74 [0.64 , 0.86]**
Heterogeneity: Chi² = 2.71, df = 6 (P = 0.84); I² = 0%						
Test for overall effect: Z = 3.91 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%						

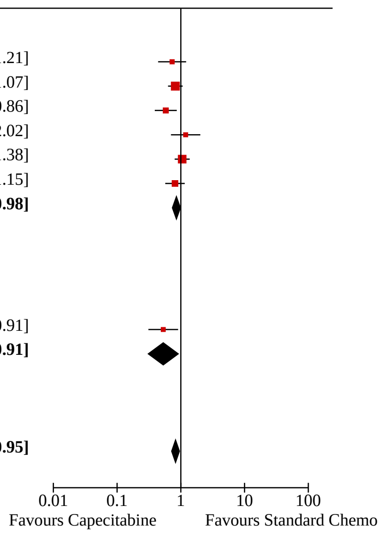


Footnotes

(1) GEICAM/200310 - calculated using REVMAN (combined hazard ratio of ER-/HER2+ and TNBC)

Analysis 6.4. Comparison 6: Adjuvant All: Sensitivity analysis of combining DFS and RFS, Outcome 4: DFS and RFS: Triple negative

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Standard Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
6.4.1 DFS						
CBCSG-10	-0.3147	0.2583	273	288	7.3%	0.73 [0.44 , 1.21]
CIBOMA 2004-01	-0.1985	0.1345	448	428	27.0%	0.82 [0.63 , 1.07]
CREATE-X	-0.5447	0.2025	443	444	11.9%	0.58 [0.39 , 0.86]
GEICAM 2003-10	0.174	0.2707	95	71	6.7%	1.19 [0.70 , 2.02]
TACT2	0.0488	0.1387	419	448	25.4%	1.05 [0.80 , 1.38]
USON 01062	-0.2107	0.1793	396	384	15.2%	0.81 [0.57 , 1.15]
Subtotal (95% CI)			**2074**	**2063**	**93.5%**	**0.85 [0.74 , 0.98]**
Heterogeneity: Chi² = 7.92, df = 5 (P = 0.16); I² = 37%						
Test for overall effect: Z = 2.21 (P = 0.03)						
6.4.2 RFS						
FINXX	-0.6349	0.2736	93	109	6.5%	0.53 [0.31 , 0.91]
Subtotal (95% CI)			**93**	**109**	**6.5%**	**0.53 [0.31 , 0.91]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.32 (P = 0.02)						
Total (95% CI)			**2167**	**2172**	**100.0%**	**0.83 [0.72 , 0.95]**
Heterogeneity: Chi² = 10.73, df = 6 (P = 0.10); I² = 44%						
Test for overall effect: Z = 2.73 (P = 0.006)						
Test for subgroup differences: Chi² = 2.82, df = 1 (P = 0.09), I² = 64.5%						



Comparison 7. Adjuvant: addition or substitution of capecitabine- vs anthracycline-taxane-containing regimen

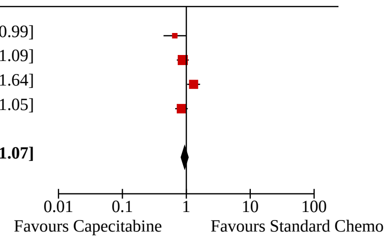
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 DFS/RFS all	4	6056	Hazard Ratio (IV, Fixed, 95% CI)	0.94 [0.83, 1.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.2 DFS/RFS hormone receptor-positive	3	3955	Hazard Ratio (IV, Fixed, 95% CI)	1.07 [0.92, 1.25]
7.3 DFS/RFS hormone receptor-negative	4	1888	Hazard Ratio (IV, Fixed, 95% CI)	0.74 [0.59, 0.93]
7.4 DFS/RFS triple-negative	4	1709	Hazard Ratio (IV, Fixed, 95% CI)	0.76 [0.61, 0.94]
7.5 OS (all)	4	6056	Hazard Ratio (IV, Fixed, 95% CI)	0.83 [0.71, 0.96]
7.6 OS hormone receptor-positive	2	2796	Hazard Ratio (IV, Fixed, 95% CI)	0.88 [0.69, 1.13]
7.7 OS hormone receptor-negative	3	1669	Hazard Ratio (IV, Fixed, 95% CI)	0.66 [0.49, 0.88]
7.8 OS triple-negative breast	3	1543	Hazard Ratio (IV, Fixed, 95% CI)	0.61 [0.46, 0.82]

Analysis 7.1. Comparison 7: Adjuvant: addition or substitution of capecitabine- vs anthracycline-taxane-containing regimen, Outcome 1: DFS/RFS all

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Standard Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CBCSG-10	-0.4155	0.2069	273	288	9.2%	0.66 [0.44 , 0.99]
FINXX	-0.1278	0.1095	753	747	33.0%	0.88 [0.71 , 1.09]
GEICAM 2003-10	0.2624	0.1188	715	669	28.0%	1.30 [1.03 , 1.64]
USON 01062	-0.1744	0.1154	1307	1304	29.7%	0.84 [0.67 , 1.05]
Total (95% CI)			**3048**	**3008**	**100.0%**	**0.94 [0.83 , 1.07]**

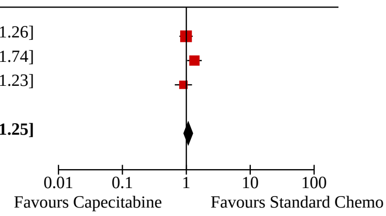
Heterogeneity: Chi² = 11.68, df = 3 (P = 0.009); I² = 74%
Test for overall effect: Z = 0.94 (P = 0.35)
Test for subgroup differences: Not applicable



Analysis 7.2. Comparison 7: Adjuvant: addition or substitution of capecitabine- vs anthracycline-taxane-containing regimen, Outcome 2: DFS/RFS hormone receptor-positive

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Standard Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
FINXX	-0.0101	0.1216	597	574	41.5%	0.99 [0.78 , 1.26]
GEICAM 2003-10 (1)	0.2927	0.1342	594	565	34.0%	1.34 [1.03 , 1.74]
USON 01062	-0.1054	0.1582	808	817	24.5%	0.90 [0.66 , 1.23]
Total (95% CI)			**1999**	**1956**	**100.0%**	**1.07 [0.92 , 1.25]**

Heterogeneity: Chi² = 4.42, df = 2 (P = 0.11); I² = 55%
Test for overall effect: Z = 0.89 (P = 0.37)
Test for subgroup differences: Not applicable

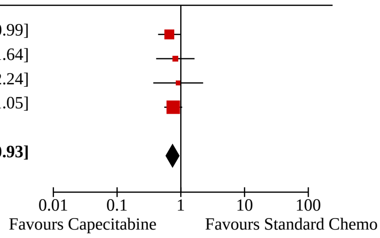


Footnotes
(1) GEICAM/200310 - calculated using REVMAN (combined hazard ratio of ER+/HER2- and ER+/HER2+)

Analysis 7.3. Comparison 7: Adjuvant: addition or substitution of capecitabine- vs anthracycline-taxane-containing regimen, Outcome 3: DFS/RFS hormone receptor-negative

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Standard Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CBCSG-10	-0.4155	0.2069	273	288	32.1%	0.66 [0.44 , 0.99]
FINXX	-0.1985	0.3537	61	61	11.0%	0.82 [0.41 , 1.64]
GEICAM 2003-10 (1)	-0.0943	0.4592	121	98	6.5%	0.91 [0.37 , 2.24]
USON 01062	-0.2744	0.165	499	487	50.4%	0.76 [0.55 , 1.05]
Total (95% CI)			**954**	**934**	**100.0%**	**0.74 [0.59 , 0.93]**

Heterogeneity: Chi² = 0.62, df = 3 (P = 0.89); I² = 0%
Test for overall effect: Z = 2.56 (P = 0.01)
Test for subgroup differences: Not applicable

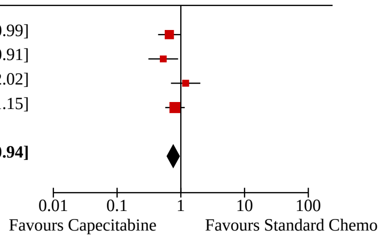


Footnotes
(1) GEICAM/200310 - calculated using REVMAN (combined hazard ratio of ER-/HER2+ and TNBC)

Analysis 7.4. Comparison 7: Adjuvant: addition or substitution of capecitabine- vs anthracycline-taxane-containing regimen, Outcome 4: DFS/RFS triple-negative

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Standard Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CBCSG-10	-0.4155	0.2069	273	288	28.7%	0.66 [0.44 , 0.99]
FINXX	-0.6349	0.2736	93	109	16.4%	0.53 [0.31 , 0.91]
GEICAM 2003-10	0.174	0.2707	95	71	16.8%	1.19 [0.70 , 2.02]
USON 01062	-0.2107	0.1793	396	384	38.2%	0.81 [0.57 , 1.15]
Total (95% CI)			**857**	**852**	**100.0%**	**0.76 [0.61 , 0.94]**

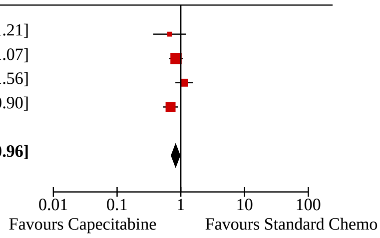
Heterogeneity: Chi² = 5.07, df = 3 (P = 0.17); I² = 41%
Test for overall effect: Z = 2.48 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 7.5. Comparison 7: Adjuvant: addition or substitution of capecitabine- vs anthracycline-taxane-containing regimen, Outcome 5: OS (all)

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Standard Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CBCSG-10	-0.4005	0.303	273	288	6.4%	0.67 [0.37 , 1.21]
FINXX	-0.1744	0.123	753	747	39.0%	0.84 [0.66 , 1.07]
GEICAM 2003-10	0.1222	0.1636	715	669	22.0%	1.13 [0.82 , 1.56]
USON 01062	-0.3711	0.1346	1307	1304	32.6%	0.69 [0.53 , 0.90]
Total (95% CI)			**3048**	**3008**	**100.0%**	**0.83 [0.71 , 0.96]**

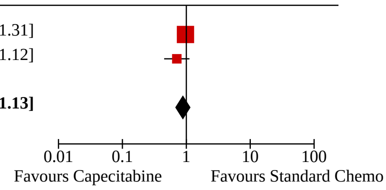
Heterogeneity: Chi² = 5.95, df = 3 (P = 0.11); I² = 50%
Test for overall effect: Z = 2.44 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 7.6. Comparison 7: Adjuvant: addition or substitution of capecitabine- vs anthracycline-taxane-containing regimen, Outcome 6: OS hormone receptor-positive

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Standard Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
FINXX	-0.0305	0.1521	597	574	70.1%	0.97 [0.72 , 1.31]
USON 01062	-0.3425	0.2327	808	817	29.9%	0.71 [0.45 , 1.12]
Total (95% CI)			**1405**	**1391**	**100.0%**	**0.88 [0.69 , 1.13]**

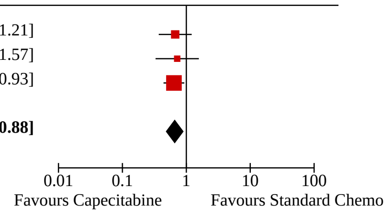
Heterogeneity: Chi² = 1.26, df = 1 (P = 0.26); I² = 21%
Test for overall effect: Z = 0.97 (P = 0.33)
Test for subgroup differences: Not applicable



Analysis 7.7. Comparison 7: Adjuvant: addition or substitution of capecitabine- vs anthracycline-taxane-containing regimen, Outcome 7: OS hormone receptor-negative

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Standard Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CBCSG-10	-0.4005	0.303	273	288	24.4%	0.67 [0.37 , 1.21]
FINXX	-0.3285	0.398	61	61	14.2%	0.72 [0.33 , 1.57]
USON 01062	-0.4463	0.1912	499	487	61.4%	0.64 [0.44 , 0.93]
Total (95% CI)			**833**	**836**	**100.0%**	**0.66 [0.49 , 0.88]**

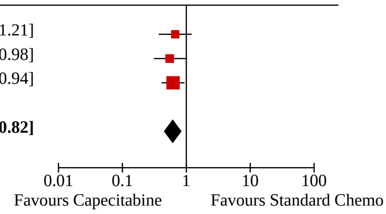
Heterogeneity: Chi² = 0.08, df = 2 (P = 0.96); I² = 0%
Test for overall effect: Z = 2.79 (P = 0.005)
Test for subgroup differences: Not applicable



Analysis 7.8. Comparison 7: Adjuvant: addition or substitution of capecitabine- vs anthracycline-taxane-containing regimen, Outcome 8: OS triple-negative breast

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Standard Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CBCSG-10	-0.4005	0.303	273	288	24.2%	0.67 [0.37 , 1.21]
FINXX	-0.5978	0.2925	93	109	25.9%	0.55 [0.31 , 0.98]
USON 01062	-0.478	0.211	396	384	49.9%	0.62 [0.41 , 0.94]
Total (95% CI)			**762**	**781**	**100.0%**	**0.61 [0.46 , 0.82]**

Heterogeneity: Chi² = 0.23, df = 2 (P = 0.89); I² = 0%
Test for overall effect: Z = 3.29 (P = 0.0010)
Test for subgroup differences: Not applicable



Comparison 8. Adjuvant: capecitabine monotherapy vs chemotherapy/other

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 DFS	4	6780	Hazard Ratio (IV, Fixed, 95% CI)	0.91 [0.82, 1.01]
8.2 DFS hormone receptor-positive	2	1986	Hazard Ratio (IV, Fixed, 95% CI)	0.96 [0.78, 1.18]
8.3 DFS hormone receptor-negative	4	2157	Hazard Ratio (IV, Fixed, 95% CI)	0.84 [0.72, 0.98]
8.4 DFS triple-negative	3	1898	Hazard Ratio (IV, Fixed, 95% CI)	0.85 [0.71, 1.01]

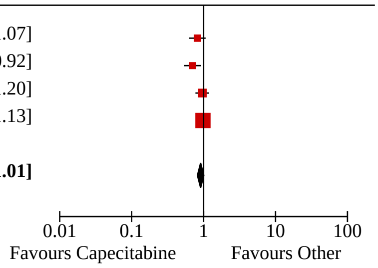
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.5 OS	4	7512	Hazard Ratio (IV, Fixed, 95% CI)	0.93 [0.83, 1.05]
8.6 OS hormone receptor-positive	1	887	Hazard Ratio (IV, Fixed, 95% CI)	0.73 [0.38, 1.40]
8.7 OS hormone receptor-negative	2	1763	Hazard Ratio (IV, Fixed, 95% CI)	0.79 [0.59, 1.05]
8.8 OS triple-negative	2	1763	Hazard Ratio (IV, Fixed, 95% CI)	0.79 [0.59, 1.05]

Analysis 8.1. Comparison 8: Adjuvant: capecitabine monotherapy vs chemotherapy/other, Outcome 1: DFS

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CIBOMA 2004-01	-0.1985	0.1345	71	73	14.8%	0.82 [0.63 , 1.07]
CREATE-X	-0.3567	0.1419	443	444	13.3%	0.70 [0.53 , 0.92]
ICE	-0.0408	0.1125	681	677	21.1%	0.96 [0.77 , 1.20]
TACT2	-0.0202	0.0726	2189	2202	50.8%	0.98 [0.85 , 1.13]
Total (95% CI)			**3384**	**3396**	**100.0%**	**0.91 [0.82 , 1.01]**

Heterogeneity: Chi² = 5.29, df = 3 (P = 0.15); I² = 43%
Test for overall effect: Z = 1.85 (P = 0.06)
Test for subgroup differences: Not applicable

Hazard Ratio
IV, Fixed, 95% CI

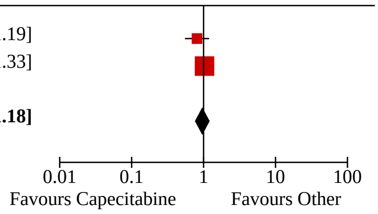


Analysis 8.2. Comparison 8: Adjuvant: capecitabine monotherapy vs chemotherapy/other, Outcome 2: DFS hormone receptor-positive

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CREATE-X	-0.2107	0.1975	443	444	29.9%	0.81 [0.55 , 1.19]
ICE	0.0296	0.1289	551	548	70.1%	1.03 [0.80 , 1.33]
Total (95% CI)			**994**	**992**	**100.0%**	**0.96 [0.78 , 1.18]**

Heterogeneity: Chi² = 1.04, df = 1 (P = 0.31); I² = 4%
Test for overall effect: Z = 0.39 (P = 0.70)
Test for subgroup differences: Not applicable

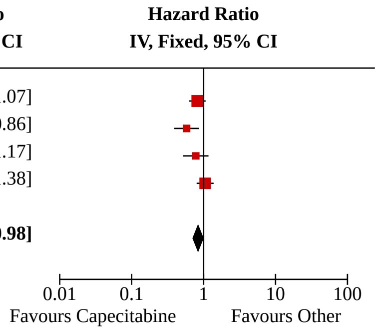
Hazard Ratio
IV, Fixed, 95% CI



Analysis 8.3. Comparison 8: Adjuvant: capecitabine monotherapy vs chemotherapy/other, Outcome 3: DFS hormone receptor-negative

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CIBOMA 2004-01	-0.1985	0.1345	71	73	35.7%	0.82 [0.63 , 1.07]
CREATE-X	-0.5447	0.2025	443	444	15.7%	0.58 [0.39 , 0.86]
ICE	-0.2485	0.2069	130	129	15.1%	0.78 [0.52 , 1.17]
TACT2	0.0488	0.1387	419	448	33.5%	1.05 [0.80 , 1.38]
Total (95% CI)			**1063**	**1094**	**100.0%**	**0.84 [0.72 , 0.98]**

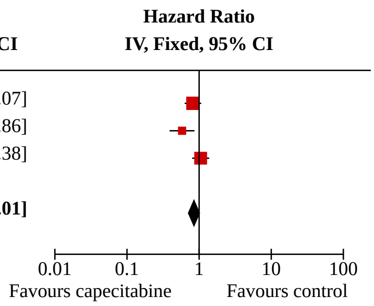
Heterogeneity: Chi² = 6.09, df = 3 (P = 0.11); I² = 51%
Test for overall effect: Z = 2.21 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 8.4. Comparison 8: Adjuvant: capecitabine monotherapy vs chemotherapy/other, Outcome 4: DFS triple-negative

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CIBOMA 2004-01	-0.1985	0.1345	71	73	42.0%	0.82 [0.63 , 1.07]
CREATE-X	-0.5447	0.2025	443	444	18.5%	0.58 [0.39 , 0.86]
TACT2	0.0488	0.1387	419	448	39.5%	1.05 [0.80 , 1.38]
Total (95% CI)			**933**	**965**	**100.0%**	**0.85 [0.71 , 1.01]**

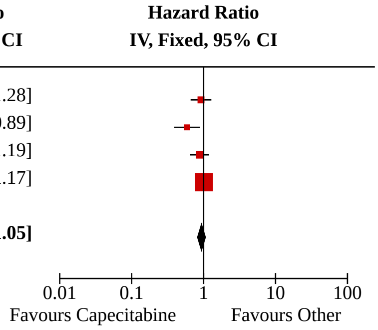
Heterogeneity: Chi² = 5.95, df = 2 (P = 0.05); I² = 66%
Test for overall effect: Z = 1.89 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 8.5. Comparison 8: Adjuvant: capecitabine monotherapy vs chemotherapy/other, Outcome 5: OS

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Other Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CIBOMA 2004-01	-0.0834	0.1695	448	428	12.8%	0.92 [0.66 , 1.28]
CREATE-X	-0.5276	0.2112	443	444	8.3%	0.59 [0.39 , 0.89]
ICE	-0.1278	0.1546	681	677	15.4%	0.88 [0.65 , 1.19]
TACT2	0.01	0.0761	2189	2202	63.5%	1.01 [0.87 , 1.17]
Total (95% CI)			**3761**	**3751**	**100.0%**	**0.93 [0.83 , 1.05]**

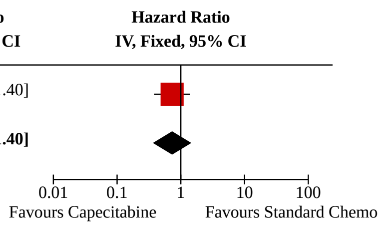
Heterogeneity: Chi² = 5.94, df = 3 (P = 0.11); I² = 50%
Test for overall effect: Z = 1.11 (P = 0.27)
Test for subgroup differences: Not applicable



Analysis 8.6. Comparison 8: Adjuvant: capecitabine monotherapy vs chemotherapy/other, Outcome 6: OS hormone receptor-positive

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Standard Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CREATE-X	-0.3147	0.3331	443	444	100.0%	0.73 [0.38 , 1.40]
Total (95% CI)			**443**	**444**	**100.0%**	**0.73 [0.38 , 1.40]**

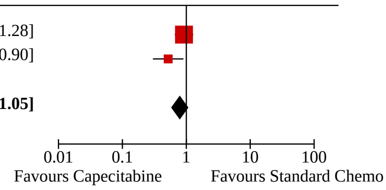
Heterogeneity: Not applicable
Test for overall effect: Z = 0.94 (P = 0.34)
Test for subgroup differences: Not applicable



Analysis 8.7. Comparison 8: Adjuvant: capecitabine monotherapy vs chemotherapy/other, Outcome 7: OS hormone receptor-negative

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Standard Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CIBOMA 2004-01	-0.0834	0.1695	448	428	73.3%	0.92 [0.66 , 1.28]
CREATE-X	-0.6539	0.2806	443	444	26.7%	0.52 [0.30 , 0.90]
Total (95% CI)			**891**	**872**	**100.0%**	**0.79 [0.59 , 1.05]**

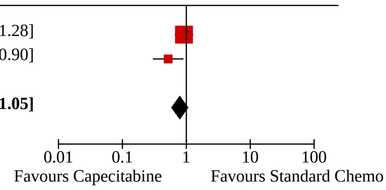
Heterogeneity: Chi² = 3.03, df = 1 (P = 0.08); I² = 67%
Test for overall effect: Z = 1.63 (P = 0.10)
Test for subgroup differences: Not applicable



Analysis 8.8. Comparison 8: Adjuvant: capecitabine monotherapy vs chemotherapy/other, Outcome 8: OS triple-negative

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Standard Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CIBOMA 2004-01	-0.0834	0.1695	448	428	73.3%	0.92 [0.66 , 1.28]
CREATE-X	-0.6539	0.2806	443	444	26.7%	0.52 [0.30 , 0.90]
Total (95% CI)			**891**	**872**	**100.0%**	**0.79 [0.59 , 1.05]**

Heterogeneity: Chi² = 3.03, df = 1 (P = 0.08); I² = 67%
Test for overall effect: Z = 1.63 (P = 0.10)
Test for subgroup differences: Not applicable



Comparison 9. Neoadjuvant: addition of capecitabine vs standard chemotherapy

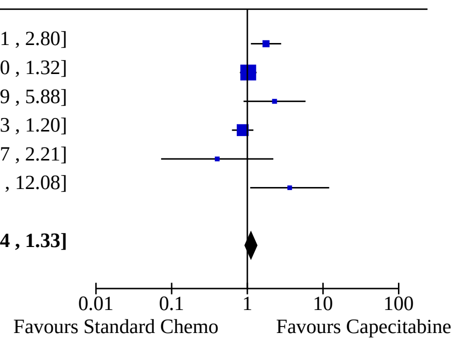
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 PCR all (breast and nodes)	6	3152	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.94, 1.33]
9.2 PCR hormone receptor-positive	4	964	Odds Ratio (IV, Fixed, 95% CI)	1.22 [0.76, 1.95]
9.3 PCR hormone receptor-negative	4	646	Odds Ratio (IV, Random, 95% CI)	1.28 [0.61, 2.66]
9.4 PCR triple-negative (breast and nodes)	4	1063	Odds Ratio (IV, Fixed, 95% CI)	1.03 [0.72, 1.46]
9.5 DFS all	4	2499	Hazard Ratio (IV, Fixed, 95% CI)	1.02 [0.86, 1.21]
9.6 OS all	4	2499	Hazard Ratio (IV, Fixed, 95% CI)	0.97 [0.77, 1.23]
9.7 AE - Anaemia	3	2686	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.54, 1.24]
9.8 AE - Neutropenia	5	3021	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.69, 1.00]
9.9 AE - Febrile neutropenia	4	2890	Odds Ratio (M-H, Fixed, 95% CI)	1.31 [0.97, 1.77]
9.10 AE - Thrombocytopenia	3	2686	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.54, 1.82]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.11 AE - Hand-foot syndrome	5	3021	Odds Ratio (M-H, Fixed, 95% CI)	6.77 [4.89, 9.38]
9.12 AE - Mucositis	5	3021	Odds Ratio (M-H, Fixed, 95% CI)	1.53 [1.11, 2.10]
9.13 AE - Diarrhoea	3	2686	Odds Ratio (M-H, Fixed, 95% CI)	1.95 [1.32, 2.89]
9.14 AE - Ischaemic heart disease	2	2215	Odds Ratio (M-H, Fixed, 95% CI)	2.26 [0.37, 13.86]
9.15 AE - Treatment-related death	4	3222	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.17, 2.04]

Analysis 9.1. Comparison 9: Neoadjuvant: addition of capecitabine vs standard chemotherapy, Outcome 1: PCR all (breast and nodes)

Study or Subgroup	Capecitabine Events	Capecitabine Total	Standard Chemo Events	Standard Chemo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ABCSG-24	57	270	35	266	11.7%	1.77 [1.11 , 2.80]
GeparQuattro	245	950	119	471	49.8%	1.03 [0.80 , 1.32]
Lee 2008	15	103	7	101	2.5%	2.29 [0.89 , 5.88]
NSABP-40	91	393	101	392	32.8%	0.87 [0.63 , 1.20]
Yoo 2015	2	36	5	39	1.9%	0.40 [0.07 , 2.21]
Zhang 2016	11	61	4	70	1.3%	3.63 [1.09 , 12.08]
Total (95% CI)		**1813**		**1339**	**100.0%**	**1.12 [0.94 , 1.33]**
Total events:	421		271			

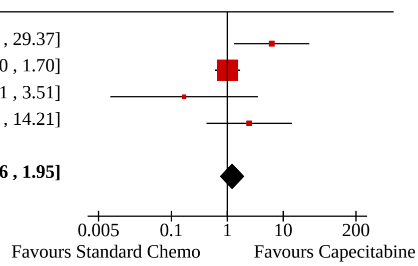
Heterogeneity: Chi² = 13.82, df = 5 (P = 0.02); I² = 64%
Test for overall effect: Z = 1.22 (P = 0.22)
Test for subgroup differences: Not applicable



Analysis 9.2. Comparison 9: Neoadjuvant: addition of capecitabine vs standard chemotherapy, Outcome 2: PCR hormone receptor-positive

Study or Subgroup	log[OR]	SE	Capecitabine Total	Standard Chemo Total	Weight	Odds Ratio IV, Fixed, 95% CI
Lee 2008	1.8288	0.7915	64	62	9.2%	6.23 [1.32 , 29.37]
NSABP-40 (1)	0.0099	0.2657	237	479	81.3%	1.01 [0.60 , 1.70]
Yoo 2015	-1.7789	1.5484	16	22	2.4%	0.17 [0.01 , 3.51]
Zhang 2016	0.899	0.8954	39	45	7.2%	2.46 [0.42 , 14.21]
Total (95% CI)			**356**	**608**	**100.0%**	**1.22 [0.76 , 1.95]**

Heterogeneity: Chi² = 6.99, df = 3 (P = 0.07); I² = 57%
Test for overall effect: Z = 0.82 (P = 0.41)
Test for subgroup differences: Not applicable



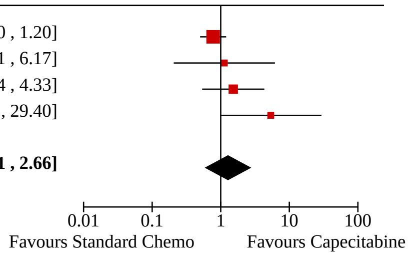
Footnotes

(1) Presented as OR as NSABP-40 (2012 supplement) only reported as p values (no N values provided)

Analysis 9.3. Comparison 9: Neoadjuvant: addition of capecitabine vs standard chemotherapy, Outcome 3: PCR hormone receptor-negative

Study or Subgroup	log[OR]	SE	Capecitabine Total	Standard Chemo Total	Weight	Odds Ratio IV, Random, 95% CI
NSABP-40 (1)	-0.2554	0.2233	168	322	46.0%	0.77 [0.50 , 1.20]
Yoo 2015	0.1206	0.8667	17	14	14.0%	1.13 [0.21 , 6.17]
Lee 2008	0.4202	0.5328	39	39	26.1%	1.52 [0.54 , 4.33]
Zhang 2016	1.6802	0.8678	22	25	14.0%	5.37 [0.98 , 29.40]
Total (95% CI)			**246**	**400**	**100.0%**	**1.28 [0.61 , 2.66]**

Heterogeneity: Tau² = 0.26; Chi² = 5.64, df = 3 (P = 0.13); I² = 47%
Test for overall effect: Z = 0.65 (P = 0.52)
Test for subgroup differences: Not applicable

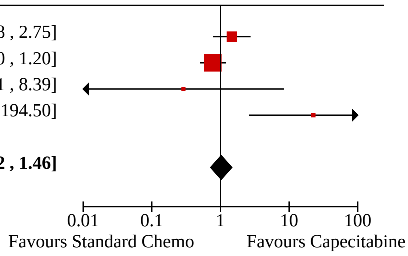


Footnotes
(1) Presented as OR as NSABP-40 (2012 supplement) only presented as p values (no N values)

Analysis 9.4. Comparison 9: Neoadjuvant: addition of capecitabine vs standard chemotherapy, Outcome 4: PCR triple-negative (breast and nodes)

Study or Subgroup	log[OR]	SE	Capecitabine Total	Standard Chemo Total	Weight	Odds Ratio IV, Fixed, 95% CI
ABCSG-24	0.384	0.3196	270	266	31.6%	1.47 [0.78 , 2.75]
NSABP-40 (1)	-0.2554	0.2233	168	322	64.7%	0.77 [0.50 , 1.20]
Yoo 2015	-1.2417	1.7187	7	7	1.1%	0.29 [0.01 , 8.39]
Zhang 2016	3.1135	1.1005	12	11	2.7%	22.50 [2.60 , 194.50]
Total (95% CI)			**457**	**606**	**100.0%**	**1.03 [0.72 , 1.46]**

Heterogeneity: Chi² = 11.26, df = 3 (P = 0.01); I² = 73%
Test for overall effect: Z = 0.14 (P = 0.89)
Test for subgroup differences: Not applicable

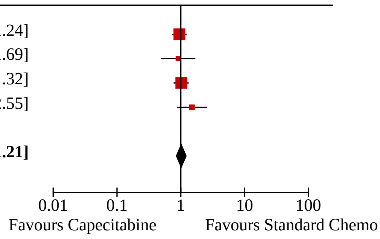


Footnotes
(1) Presented as OR as NSABP-40 (2012 supplement) only presented as p values (no N values) - all patients in NSABP-40 were HER2 neg, thus all HRneg = TNBC

Analysis 9.5. Comparison 9: Neoadjuvant: addition of capecitabine vs standard chemotherapy, Outcome 5: DFS all

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Standard Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
GeparQuattro	-0.0513	0.1344	950	471	42.3%	0.95 [0.73 , 1.24]
Lee 2008 (1)	-0.0943	0.3158	106	103	7.7%	0.91 [0.49 , 1.69]
NSABP-40	0.01	0.1384	400	394	39.9%	1.01 [0.77 , 1.32]
Yoo 2015 (2)	0.3988	0.2745	36	39	10.1%	1.49 [0.87 , 2.55]
Total (95% CI)			**1492**	**1007**	**100.0%**	**1.02 [0.86 , 1.21]**

Heterogeneity: Chi² = 2.32, df = 3 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.18 (P = 0.86)
Test for subgroup differences: Not applicable

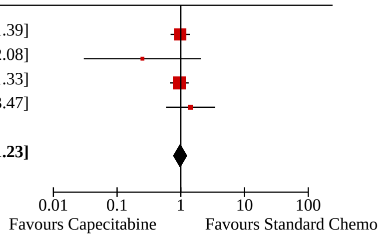


Footnotes
(1) Lee: HR 0.91 (95 CI 0.49-1.7); median f/up 37months; HR for LEE calculated using spreadsheet tool by Tierney
(2) Yoo: HR 1.49 (95CI 0.87-2.56); median f/up - 53.7months; HR for YOO calculated using WebPlotdigitizer and spreadsheet tool by Tierney

Analysis 9.6. Comparison 9: Neoadjuvant: addition of capecitabine vs standard chemotherapy, Outcome 6: OS all

Study or Subgroup	log[Hazard Ratio]	SE	Capecitabine Total	Standard Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
GeparQuattro	-0.0202	0.179	950	471	43.8%	0.98 [0.69 , 1.39]
Lee 2008 (1)	-1.3863	1.0818	106	103	1.2%	0.25 [0.03 , 2.08]
NSABP-40	-0.0513	0.1706	400	394	48.2%	0.95 [0.68 , 1.33]
Yoo 2015 (2)	0.3577	0.4517	36	39	6.9%	1.43 [0.59 , 3.47]
Total (95% CI)			**1492**	**1007**	**100.0%**	**0.97 [0.77 , 1.23]**

Heterogeneity: Chi² = 2.33, df = 3 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.22 (P = 0.83)
Test for subgroup differences: Not applicable



Footnotes

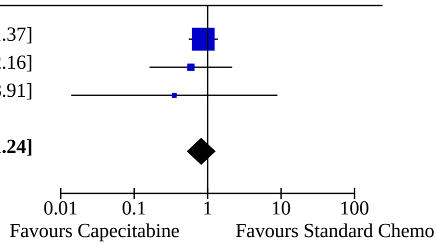
(1) Lee: HR 0.25 (95CI 0.03-2.12); median f/up - 37months; HR for Lee calculated using spreadsheet tool by Tierney (taking into account 4 yr survival)

(2) Yoo: HR 1.43 (95CI 0.59-3.49); median f/up - 53.7months; HR for YOO calculated using WebPlotdigitizer and spreadsheet tool by Tierney

Analysis 9.7. Comparison 9: Neoadjuvant: addition of capecitabine vs standard chemotherapy, Outcome 7: AE - Anaemia

Study or Subgroup	Capecitabine Events	Capecitabine Total	Standard Chemo Events	Standard Chemo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
GeparQuattro	55	950	31	471	82.9%	0.87 [0.55 , 1.37]
NSABP-40	3	399	10	791	14.1%	0.59 [0.16 , 2.16]
Yoo 2015	0	36	1	39	3.0%	0.35 [0.01 , 8.91]
Total (95% CI)		**1385**		**1301**	**100.0%**	**0.82 [0.54 , 1.24]**
Total events:	58		42			

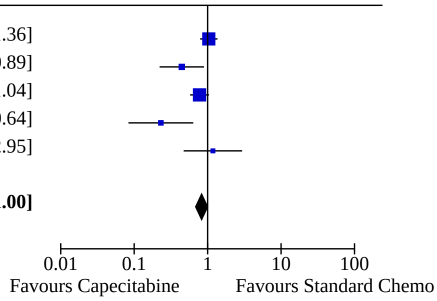
Heterogeneity: Chi² = 0.58, df = 2 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.94 (P = 0.35)
Test for subgroup differences: Not applicable



Analysis 9.8. Comparison 9: Neoadjuvant: addition of capecitabine vs standard chemotherapy, Outcome 8: AE - Neutropenia

Study or Subgroup	Capecitabine Events	Capecitabine Total	Standard Chemo Events	Standard Chemo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
GeparQuattro	756	950	372	471	40.2%	1.04 [0.79 , 1.36]
Lee 2008	74	103	86	101	9.7%	0.45 [0.22 , 0.89]
NSABP-40	79	399	191	791	40.6%	0.78 [0.58 , 1.04]
Yoo 2015	17	36	31	39	6.2%	0.23 [0.08 , 0.64]
Zhang 2016	11	61	11	70	3.3%	1.18 [0.47 , 2.95]
Total (95% CI)		**1549**		**1472**	**100.0%**	**0.83 [0.69 , 1.00]**
Total events:	937		691			

Heterogeneity: Chi² = 12.51, df = 4 (P = 0.01); I² = 68%
Test for overall effect: Z = 2.00 (P = 0.04)
Test for subgroup differences: Not applicable

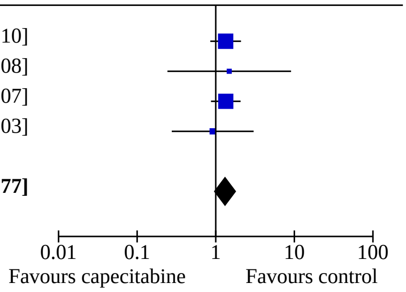


Analysis 9.9. Comparison 9: Neoadjuvant: addition of capecitabine vs standard chemotherapy, Outcome 9: AE - Febrile neutropenia

Study or Subgroup	Capecitabine Events	Capecitabine Total	Standard Chemo Events	Standard Chemo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
GeparQuattro	74	950	28	471	45.3%	1.34 [0.85 , 2.10]
Lee 2008	3	103	2	101	2.6%	1.49 [0.24 , 9.08]
NSABP-40	37	399	56	791	44.7%	1.34 [0.87 , 2.07]
Yoo 2015	6	36	7	39	7.4%	0.91 [0.28 , 3.03]
Total (95% CI)		**1488**		**1402**	**100.0%**	**1.31 [0.97 , 1.77]**
Total events:	120		93			

Heterogeneity: Chi² = 0.38, df = 3 (P = 0.94); I² = 0%
Test for overall effect: Z = 1.78 (P = 0.07)
Test for subgroup differences: Not applicable

Odds Ratio
M-H, Fixed, 95% CI

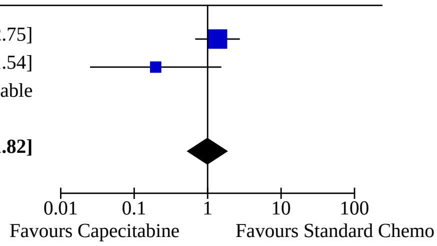


Analysis 9.10. Comparison 9: Neoadjuvant: addition of capecitabine vs standard chemotherapy, Outcome 10: AE - Thrombocytopenia

Study or Subgroup	Capecitabine Events	Capecitabine Total	Standard Chemo Events	Standard Chemo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
GeparQuattro	30	950	11	471	68.0%	1.36 [0.68 , 2.75]
NSABP-40	1	399	10	791	32.0%	0.20 [0.03 , 1.54]
Yoo 2015	0	36	0	39		Not estimable
Total (95% CI)		**1385**		**1301**	**100.0%**	**0.99 [0.54 , 1.82]**
Total events:	31		21			

Heterogeneity: Chi² = 3.18, df = 1 (P = 0.07); I² = 69%
Test for overall effect: Z = 0.03 (P = 0.98)
Test for subgroup differences: Not applicable

Odds Ratio
M-H, Fixed, 95% CI

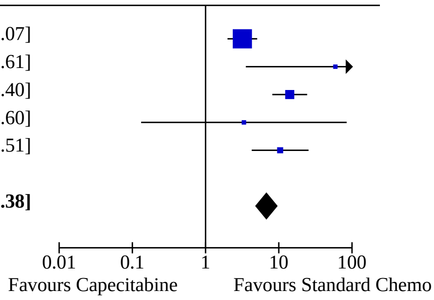


Analysis 9.11. Comparison 9: Neoadjuvant: addition of capecitabine vs standard chemotherapy, Outcome 11: AE - Hand-foot syndrome

Study or Subgroup	Capecitabine Events	Capecitabine Total	Standard Chemo Events	Standard Chemo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
GeparQuattro	128	950	22	471	67.4%	3.18 [1.99 , 5.07]
Lee 2008	23	103	0	101	1.0%	59.26 [3.55 , 990.61]
NSABP-40	90	399	16	791	22.0%	14.11 [8.16 , 24.40]
Yoo 2015	1	36	0	39	1.2%	3.34 [0.13 , 84.60]
Zhang 2016	35	61	8	70	8.4%	10.43 [4.27 , 25.51]
Total (95% CI)		**1549**		**1472**	**100.0%**	**6.77 [4.89 , 9.38]**
Total events:	277		46			

Heterogeneity: Chi² = 20.35, df = 4 (P = 0.0004); I² = 80%
Test for overall effect: Z = 11.52 (P < 0.00001)
Test for subgroup differences: Not applicable

Odds Ratio
M-H, Fixed, 95% CI

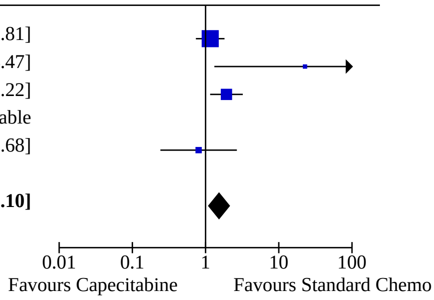


Analysis 9.12. Comparison 9: Neoadjuvant: addition of capecitabine vs standard chemotherapy, Outcome 12: AE - Mucositis

Study or Subgroup	Capecitabine Events	Capecitabine Total	Standard Chemo Events	Standard Chemo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
GeparQuattro	67	950	29	471	57.8%	1.16 [0.74 , 1.81]
Lee 2008	10	103	0	101	0.7%	22.80 [1.32 , 394.47]
NSABP-40	30	399	32	791	31.8%	1.93 [1.15 , 3.22]
Yoo 2015	0	36	0	39		Not estimable
Zhang 2016	5	61	7	70	9.6%	0.80 [0.24 , 2.68]
Total (95% CI)		**1549**		**1472**	**100.0%**	**1.53 [1.11 , 2.10]**
Total events:	112		68			

Heterogeneity: Chi² = 6.80, df = 3 (P = 0.08); I² = 56%
Test for overall effect: Z = 2.59 (P = 0.010)
Test for subgroup differences: Not applicable

Odds Ratio M-H, Fixed, 95% CI

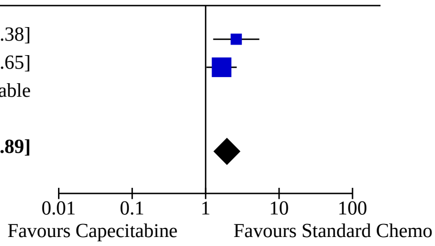


Analysis 9.13. Comparison 9: Neoadjuvant: addition of capecitabine vs standard chemotherapy, Outcome 13: AE - Diarrhoea

Study or Subgroup	Capecitabine Events	Capecitabine Total	Standard Chemo Events	Standard Chemo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
GeparQuattro	46	950	9	471	31.2%	2.61 [1.27 , 5.38]
NSABP-40	33	399	41	791	68.8%	1.65 [1.03 , 2.65]
Yoo 2015	0	36	0	39		Not estimable
Total (95% CI)		**1385**		**1301**	**100.0%**	**1.95 [1.32 , 2.89]**
Total events:	79		50			

Heterogeneity: Chi² = 1.10, df = 1 (P = 0.29); I² = 9%
Test for overall effect: Z = 3.34 (P = 0.0008)
Test for subgroup differences: Not applicable

Odds Ratio M-H, Fixed, 95% CI

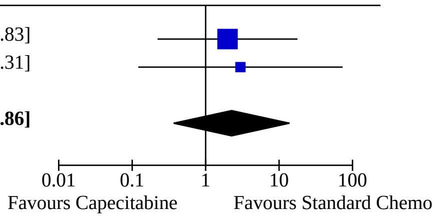


Analysis 9.14. Comparison 9: Neoadjuvant: addition of capecitabine vs standard chemotherapy, Outcome 14: AE - Ischaemic heart disease

Study or Subgroup	Capecitabine Events	Capecitabine Total	Standard Chemo Events	Standard Chemo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
GeparQuattro	4	950	1	471	72.7%	1.99 [0.22 , 17.83]
NSABP-40	1	399	0	395	27.3%	2.98 [0.12 , 73.31]
Total (95% CI)		**1349**		**866**	**100.0%**	**2.26 [0.37 , 13.86]**
Total events:	5		1			

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.88 (P = 0.38)
Test for subgroup differences: Not applicable

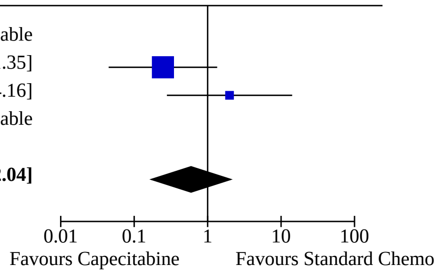
Odds Ratio M-H, Fixed, 95% CI



Analysis 9.15. Comparison 9: Neoadjuvant: addition of capecitabine vs standard chemotherapy, Outcome 15: AE - Treatment-related death

Study or Subgroup	Capecitabine Events	Capecitabine Total	Standard Chemo Events	Standard Chemo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ABCSG-24 (1)	0	270	0	266		Not estimable
GeparQuattro	2	950	4	471	80.0%	0.25 [0.04 , 1.35]
NSABP-40	2	399	2	791	20.0%	1.99 [0.28 , 14.16]
Yoo 2015	0	36	0	39		Not estimable
Total (95% CI)		**1655**		**1567**	**100.0%**	**0.59 [0.17 , 2.04]**
Total events:	4		6			

Odds Ratio M-H, Fixed, 95% CI



Heterogeneity: Chi² = 2.48, df = 1 (P = 0.12); I² = 60%
Test for overall effect: Z = 0.83 (P = 0.41)
Test for subgroup differences: Not applicable

Footnotes
(1) ABCSG24 - 3 deaths, not treatment related

ADDITIONAL TABLES

Table 1. Overview of included studies summarising treatment regimens

Study	Setting	N	Capecitabine-containing arm	Comparator arm
ABCSG-24	Neoadjuvant	536	Capecitabine + epirubicin + docetaxel	Epirubicin + docetaxel
GeparQuattro	Neoadjuvant	1421	Epirubicin + cyclophosphamide > docetaxel > capecitabine or epirubicin + cyclophosphamide > docetaxel + capecitabine	Epirubicin + cyclophosphamide > docetaxel
Lee 2008	Neoadjuvant	209	Capecitabine + docetaxel	Doxorubicin + cyclophosphamide
NSABP-40	Neoadjuvant	1206	Capecitabine + docetaxel > doxorubicin + cyclophosphamide ± bevacizumab	Docetaxel or docetaxel + gemcitabine > doxorubicin + cyclophosphamide ± bevacizumab
Yoo 2015	Neoadjuvant	75	Capecitabine + vinorelbine > docetaxel	Doxorubicin + cyclophosphamide > docetaxel
Zhang 2016	Neoadjuvant	131	Capecitabine + epirubicin + cyclophosphamide	Fluorouracil + epirubicin + cyclophosphamide
CBCSG-10	Adjuvant	636	Capecitabine + docetaxel > epirubicin + cyclophosphamide + capecitabine	Docetaxel > fluorouracil + epirubicin + cyclophosphamide
CIBOMA 2004-01	Adjuvant	876	Neoadjuvant chemotherapy > adjuvant capecitabine	Observation
CREATE-X	Adjuvant	910	Neoadjuvant chemotherapy > adjuvant capecitabine	Observation

Table 1. Overview of included studies summarising treatment regimens *(Continued)*

FINXX	Adjuvant	1500	Capecitabine + docetaxel > epirubicin + cyclophosphamide + capecitabine	Docetaxel > fluorouracil + epirubicin + cyclophosphamide
GEICAM 2003-10	Adjuvant	1384	Capecitabine + epirubicin + docetaxel	Epirubicin + cyclophosphamide > docetaxel
ICE	Adjuvant	1358	Capecitabine + ibandronate	Ibandronate
TACT2	Adjuvant	4391	Capecitibine + epirubicin (dose dense or standard)	Epirubicin (dose dense or standard) > cyclophosphamide + methotrexate + fluorouracil
USON 01062	Adjuvant	2611	Doxorubicin + cyclophosphamide > docetaxel + capecitabine	Doxorubicin + cyclophosphamide > docetaxel
BOLERO6	Metastatic	309	Capecitabine	Everolimus ± exemestane
Chan 2009	Metastatic	305	Capecitabine + docetaxel	Gemcitabine + docetaxel
CHAT	Metastatic	222	Capecitabine + trastuzumab + docetaxel	Trastuzumab + docetaxel
Fan 2013	Metastatic	53	Capecitabine + docetaxel	Cisplatin + docetaxel
IMELDA	Metastatic	185	Capecitabine + bevacizumab	Bevacizumab
METRIC	Metastatic	327	Capecitabine	Glembatumumb vedotin
Pallis 2012	Metastatic	158	Capecitabine	Vinorelbine + gemcitabine
SO140999	Metastatic	511	Capecitabine + docetaxel	Docetaxel
Seidman 2011	Metastatic	489	Capecitabine + docetaxel	Gemcitabine + docetaxel
Study 301	Metastatic	1102	Capecitabine	Eribulin mesylate
TABEA	Metastatic	234	Capecitabine + bevacizumab + docetaxel OR paclitaxel	Bevacizumab + docetaxel OR paclitaxel
TURANDOT	Metastatic	564	Capecitabine + bevacizumab	Bevacizumab + paclitaxel

Table 2. Quality of life assessments in patients with metastatic breast cancer

Study	QoL collected or reported	Questionnaire and any methods used	Main results
BOLERO6	Collected as listed in NCT01783444 trial record but not reported	Not reported	Not reported

Table 2. Quality of life assessments in patients with metastatic breast cancer *(Continued)*

Chan 2009	Yes	Rotterdam Symptom Checklist at baseline and on Day 1 of each cycle	"QoL was not different between treatment arms. There was no decrease in the overall valuation of life in either arm. Additional data will be presented in a separate publication" (p 1758)
CHAT	No	N/A	N/A
Fan 2013	No	N/A	N/A
IMELDA	Yes	European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-C30, completed at screening, at randomisation, every 3 cycles before progression, and at (but not after) disease progression	"Mean change from baseline for global health score did not differ between the treatment groups (data not shown). More detailed patient-reported outcome results and exploratory analyses will be reported separately" (p 1358)
METRIC	No	N/A	N/A
Pallis 2012	No	N/A	N/A
Seidman 2011	No	N/A	N/A
SO140999	Yes	EORTC QLQ-C30 but only in selected centres, where there were validated EORTC questionnaire translations. Primary QoL analysis used the "last observation forward' approach to replacing missing data	"Analysis included 454 patients from 15 countries. Global Health Score was selected as the primary parameter for statistical testing. No significant differences between treatment arms at Day 127 were noted. There was a trend towards less deterioration of GHS in the combination arm over time" (p 2817)
Study 301	Yes	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (version 3.0) and breast module Quality of Life Questionnaire BR23 (version 1.0) at baseline, at 6 weeks, and at 3, 6, 12, 18, and 24 months, or until disease progression or initiation of other antitumour treatment. The principal prespecified outcome was overall QoL, expressed as change from baseline in Global Health Status (GHS)/QoL measured on a 0 (worst) to 100 (best) scale	"> 95% available at baseline, completion rates decreased with time in both treatment arms. GHS/QoL scores low at baseline in both eribulin and capecitabine arms. Over time, average GHS/QoL scores improved in both arms; linear-mixed and pattern-mixed model showed no significant difference between groups" (p 599)
TABEA	No	N/A	N/A
TURANDOT	Yes	EORCT QLQ-30 at baseline, at each tumour assessment (every 12 weeks), and 28 days after discontinuation of study treatment	"Baseline QoL questionnaires available from all participants in safety population in both arms. End of treatment QoL questionnaires were available from 49% in paclitaxel group and 51% in capecitabine group. Analysis of mean global health status showed no major difference between treatment groups and little change from baseline over time. Highest mean baseline symptom scores in

Table 2. Quality of life assessments in patients with metastatic breast cancer *(Continued)*

			both groups were for fatigue, pain, and insomnia; mean scores showed no meaningful increase (reflecting deterioration in QoL) over time. Mean scores for appetite loss, dyspnoea, and financial difficulties varied slightly over time with little difference between groups. Mean scores for physical, emotional, role, cognitive, and social functioning showed slight or no change over time and no differences between treatment groups" (p 130)

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer core quality of life questionnaire.
GHS: global health status.
N/A: not applicable.
QoL: quality of life.

Table 3. Toxicities for capecitabine-containing regimens vs non-capecitabine-containing regimens for metastatic breast cancer

Study	Treatment vs comparator	Febrile neutropenia		Diarrhoea		Hand-foot syndrome	
		Capecitabine regimen (n/N)	Comparator (n/N)	Capecitabine regimen (n/N)	Comparator (n/N)	Capecitabine regimen (n/N)	Comparator (n/N)
BOLERO6	Capecitabine vs everolimus + exemestane	NR	NR	8/102	5/104	28/102	1/104
Chan 2009	Capecitabine + docetaxel vs gemcitabine + docetaxel	21/150	13/152	27/150	12/152	39/150	0/152
CHAT	Capecitabine + trastuzumab + docetaxel vs trastuzumab + docetaxel	17/112	30/110	11/112	4/110	17/112	0/110
Fan 2013	Capecitabine + docetaxel vs cisplatin + docetaxel	1/26	0/27	5/26	2/27	5/26	0/27
IMELDA	Capecitabine + bevacizumab vs bevacizuamb	0/91	0/92	2/91	0/92	0/91	0/92
METRIC	Capecitabine vs glembatumumb vedotin	NR	NR	13/92	7/213	NR	7/92
Pallis 2012	Capecitabine vs vinorelbine + gemcitabine	0/74	1/74	1/74	1/74	4/74	1/74
SO140999	Capecitabine + docetaxel vs docetaxel	31/178	43/178	24/178	11/178	50/178	2/178
Seidman 2011	Capecitabine + docetaxel vs gemcitabine + docetaxel	14/226	17/237	NR	NR	57/226	3/237
Study 301	Capecitabine vs eribulin	5/546	11/544	29/546	6/544	79/546	0/544
TABEA	Capecitabine + bevacizumab + docetaxel OR paclitaxel vs bevacizumab + docetaxel OR paclitaxel	2/111	0/116	9/111	2/116	27/111	2/116
TURANDOT	Capecitabine + bevacizumab vs bevacizumab + paclitaxel	0/67	0/160	5/67	6/160	7/67	22/160

All toxicities are G3 or G4, except SO140999, for which grade of toxicity was not specified in reporting.
METRIC - 1 episode of fatal neutropenic sepsis noted in the glematumumab vedotin arm, and none in the capecitabine arm, but no rates of febrile neutropenia reported.

APPENDICES

Appendix 1. MEDLINE

1	Case-Control Studies/
2	Control Groups/
3	Matched-Pair Analysis/
4	Retrospective Studies/
5	((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.
6	or/1-5
7	Cohort Studies/
8	Longitudinal Studies/
9	Follow-Up Studies/
10	Prospective Studies/
11	Retrospective Studies/
12	cohort.ti,ab.
13	longitudinal.ti,ab.
14	prospective.ti,ab.
15	retrospective.ti,ab.
16	or/7-15
17	randomized controlled trial.pt.
18	controlled clinical trial.pt.
19	randomized.ab.
20	placebo.ab.
21	Clinical Trials as Topic/
22	randomly.ab.
23	trial.ti.
24	(crossover or cross-over).tw.
25	Pragmatic Clinical Trials as Topic/
26	pragmatic clinical trial.pt.

(Continued)

27	or/17-26
28	exp Breast Neoplasms/
29	(breast adj6 cancer$).tw.
30	(breast adj6 neoplasm$).tw.
31	(breast adj6 carcinoma$).tw.
32	(breast adj6 tumo?r$).tw.
33	or/28-32
34	exp Capecitabine/
35	(Capecitabine or xeloda).tw.
36	34 or 35
37	33 and 36
38	6 and 37
39	limit 38 to yr="2014 -Current"
40	16 and 37
41	limit 40 to yr="2014 -Current"
42	27 and 37
43	limit 42 to yr="2014 -Current"

Appendix 2. Embase

1	exp case control study/
2	case control study.ti,ab.
3	((case control or case base or case matched or retrospective) adj1 (analys* or design* or evaluation* or research or stud* or survey* or trial*)).ti,ab.
4	or/1-3
5	exp retrospective study/
6	exp prospective study/
7	((cohort or concurrent or incidence or longitudinal or followup or 'follow up' or prospective or retrospective) adj1 (analys* or design* or evaluation* or research or stud* or survey* or trial*)).ti,ab.

(Continued)

8	or/5-7
9	Randomized controlled trial/
10	Controlled clinical study/
11	Random$.ti,ab.
12	randomization/
13	intermethod comparison/
14	placebo.ti,ab.
15	(compare or compared or comparison).ti.
16	((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.
17	(open adj label).ti,ab.
18	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
19	double blind procedure/
20	parallel group$1.ti,ab.
21	(crossover or cross over).ti,ab.
22	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.
23	(assigned or allocated).ti,ab.
24	(controlled adj7 (study or design or trial)).ti,ab.
25	(volunteer or volunteers).ti,ab.
26	human experiment/
27	trial.ti.
28	or/9-27
29	exp breast/
30	exp breast disease/
31	(29 or 30) and exp neoplasm/
32	exp breast tumor/
33	exp breast cancer/
34	exp breast carcinoma/

(Continued)

35	(breast$ adj5 (neoplas$ or cancer$ or carcin$ or tumo$ or metasta$ or malig$)).ti,ab.
36	or/31-35
37	exp capecitabine/
38	(xeloda or capecitabine).tw.
39	37 or 38
40	36 and 39
41	4 and 40
42	limit 41 to (embase and yr="2014 -Current")
43	8 and 40
44	limit 43 to (embase and yr="2014 -Current")
45	28 and 40
46	limit 45 to (embase and yr="2014 -Current")

Appendix 3. CENTRAL

#1 MeSH descriptor: [Breast Neoplasms] explode all trees
#2 breast near cancer*
#3 breast near neoplasm*
#4 breast near carcinoma*
#5 breast near tumour*
#6 breast near tumor*
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 capecitabine
#9 MeSH descriptor: [Capecitabine] explode all trees
#10 xeloda
#11 #8 or #9 or #10
#12 #7 and #11 Publication Year from 2014 to 2016

Appendix 4. WHO ICTRP

Advanced search:
Title: breast cancer AND capecitabine

Appendix 5. ClinicalTrials.gov

Advanced search:
Title: breast cancer AND capecitabine

Appendix 6. Data extraction form template

- SOURCE
  - Study ID
  - Report ID
  - Review author ID
  - Citation and contact details

- ELIGIBILITY
  - Confirm eligibility
  - Reason for exclusion
- METHODS
  - Study design
  - Total study duration
  - Sample size considerations
  - Sequence generation
  - Allocation sequence concealment
  - Blinding
  - Other concerns: RE bias
- PARTICIPANTS
  - Total number
  - Diagnostic criteria including measurement of hormone receptor status (immunohistochemistry diagnostic criteria)
  - Age
  - Country
  - Co-morbidities
  - Breast cancer stage
  - Hormone receptor status (%)
    - ER- and PgR-positive (%)
    - ER-positive/PgR-negative or unknown (%)
    - ER-negative or unknown/PgR-positive (%)
    - ER- and PgR-negative (%)
    - Not assessed or unknown (%)
  - HER2 status (%) (defined by IHC 3+ and/or ISH-positive)
  - Breast cancer molecular subtype
  - For palliative treatment trials, percentage of non-capecitabine patients who subsequently crossed over to receive capecitabine following trial completion
  - For palliative treatment trials, receipt of endocrine and other targeted therapies before commencement of trial
  - For palliative treatment trials, receipt of chemotherapy before commencement of trial
- INTERVENTION AND COMPARATOR GROUPS
  - Total number of groups
  - Chemotherapy regimen, including dose
  - Co-interventions including endocrine therapy, biologic agents, radiotherapy
  - Adherence
  - Exposure
- OUTCOME MEASURES
  - Outcome measure for each of neoadjuvant, adjuvant, and palliative-intent treatment chemotherapy regimens containing capecitabine compared with regimens not containing capecitabine for women with ER-positive breast cancer
  - Outcome measure for each of neoadjuvant, adjuvant, and palliative-intent treatment chemotherapy regimens containing capecitabine compared with regimens not containing capecitabine for women with ER-negative breast cancer
- OUTCOME MEASURES - Neoadjuvant treatment
  - Primary outcome - pCR
    - Definition of pCR
  - Secondary outcomes - RFS, DFS, OS
    - Duration of follow-up
    - Definition of DFS and RFS
    - Follow-up investigations

- OUTCOME MEASURES - Adjuvant treatment
  - Primary outcome - RFS
    - Definition of RFS
    - Duration of follow-up
    - Follow-up investigations
  - Secondary outcomes - DFS, OS, BCSS
    - Definition of BCSS and DFS
    - Duration of follow-up
    - Follow-up investigations
- OUTCOME MEASURES - Palliative treatment
  - Primary outcome - ORR
    - Definition of ORR
    - Timing and nature of response investigations (CT, PET, clinical, other)
  - Secondary outcomes - OS, PFS, CBR
    - Definition of PFS, CBR
    - Duration of follow-up
    - Follow-up investigations
- OUTCOME MEASURES - Adverse events
  - Definition of specific adverse events
  - Methods of monitoring for adverse events including frequency of examination/investigation and person reporting event (clinician or patient)

- OUTCOME MEASURES - Palliative treatment
  - Primary outcome - ORR
    - Definition of ORR
    - Timing and nature of response investigations (CT, PET, clinical, other)
  - Secondary outcomes - OS, PFS, CBR
    - Definition of PFS, CBR
    - Duration of follow-up
    - Follow-up investigations
- OUTCOME MEASURES - Adverse events
  - Definitions of specific adverse events
  - Methods of monitoring for adverse events including frequency of examination/investigation and person reporting event (clinician or patient)

- RESULTS - Neoadjuvant treatment
  - Primary outcome - pCR
    - Risk ratio (RR) with 95% confidence interval (CI)
  - Secondary outcomes - DFS, RFS, OS
    - Hazard ratio (HR)
- RESULTS - Adjuvant treatment
  - Primary outcome - RFS
    - HR
  - Secondary outcomes - DFS, OS, BCSS
    - HR
- RESULTS - Palliative treatment
  - Primary outcome - ORR
    - RR with 95% CI
  - Secondary outcomes - OS, PFS, CBR
    - HR for OS, PFS
    - RR with 95% CI for CBR
- RESULTS - Adverse events
  - Cytopenias
  - Hand-foot syndrome
  - Mucositis
  - Diarrhoea
  - Ischaemic cardiac disease

- MISCELLANEOUS
  - Funding source
  - Ethical approval
  - Single-centre or multi-centre
  - Correspondence required
  - Author conclusions
  - Author conflicts of interest

WHAT'S NEW

Date	Event	Description
27 May 2021	Review declared as stable	Due to the complexity of this topic, the topic will be split into new review topics. Evidence will be presented separately for adjuvant, neoadjuvant and palliative chemotherapy.

HISTORY

Protocol first published: Issue 8, 2014
Review first published: Issue 5, 2021

CONTRIBUTIONS OF AUTHORS

- Drafting the protocol: AW
- Selection of studies: AW, PL, MB, AR
- Extraction of data from studies: AW, PL, SH, PB, AR
- Entry of data into RevMan: AW, PL, SH, PB, AR
- Carrying out the analysis: PL, SH, AR
- Interpretation of the analysis: PL, SH, AR
- Drafting of the final review: PL, SH, PB, AR
- Disagreement resolution: AR
- Update of the review: AR

DECLARATIONS OF INTEREST

SH: none related to this review. Received travel and accommodation funding for investigator meetings on unrelated trials (MK3475-716, MK3475-495, M16-289) from Merck and AbbVie.

PL: none related to this review. Received financial support to attend educational events from Roche, Pfizer and Medical Oncology Group of Australia (MOGA), and honoraria for speaking at education meetings unrelated to this submitted work from Bristol-Myers Squibb and Pfizer.

AW: none known.

MB: none known.

PB: none known.

AR: none related to this review. Received payment for developing education meeting on biosimilars from Roche, financial support for virtual registration at San Antonio Breast Cancer Symposium from Novartis and board membership from Roche, Novartis and Pfizer, and honoraria for unrelated research from Eisai.

SOURCES OF SUPPORT

Internal sources

- Royal Perth Hospital, Australia

  Salary

- Royal Perth Hospital, Cancer Research Fellowship, WA Health, Australia

  Salary
- University of Notre Dame, Australia

  Salary
- Cancer Council of WA, Australia

  Clinical Fellowship

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- Outcomes
  - Breast cancer-specific survival (BCSS) was initially planned to be collected as a secondary outcome in the adjuvant setting but was not assessed, as it was not well reported in the included studies
  - Quality of life (QoL) was not initially planned to be collected as a secondary outcome in the metastatic setting, but this was felt to be an oversight and this information was subsequently collected
- Other protocol subgroup assessments were planned including:
  - HER2 over-expression in each of neoadjuvant, adjuvant, and palliative-intent treatment groups - some trials excluded HER2-positive participants. Beyond this, although HER2 data were frequently reported across whole trial cohorts between treatment arms, they were very rarely reported within HR status-specific subgroups, rendering HER2 subgroup analysis impractical and of low utility; and
  - capecitabine as a first or subsequent line of therapy in palliative-intent treatment - the heterogeneity of design in palliative-intent trials and the paucity of data on treatment line within hormone receptor status-specific subgroups prevented assessment by treatment line per se. Comment is made on relative capecitabine utility for particular trials that specified a particular treatment line.
- Additional subgroup assessments
  - Metastatic and adjuvant settings were further subdivided into subgroups depending on how capecitabine was incorporated (i.e. monotherapy, addition to a chemotherapy regimen, or substitution into a chemotherapy regimen). Given the small number of studies in the adjuvant setting, addition and substitution were combined into a single subgroup
- Analyses
  - DFS and RFS, although defined differently in the literature and in this review, were felt to be clinically indifferent and reported in the same analysis. A sensitivity analysis was performed to minimise any bias this may have created
  - One pooled analysis was included despite the issues that could be created (i.e. uncertainty in heterogeneity of pooled effect estimates and undue weighting of pooled effect estimates) (Seidman 2014 - pooled analysis of Chan 2009 and Seidman 2011). The two studies were felt to be very similar in design and intervention, and neither study reported outcomes by hormone receptor status. This is discussed in greater detail under Sensitivity analysis and Included studies

INDEX TERMS

Medical Subject Headings (MeSH)

Antimetabolites, Antineoplastic [adverse effects] [*therapeutic use]; Antineoplastic Combined Chemotherapy Protocols [adverse effects] [*therapeutic use]; Bias; Breast Neoplasms [chemistry] [*drug therapy] [mortality] [pathology]; Capecitabine [adverse effects] [*therapeutic use]; Chemotherapy, Adjuvant; Disease-Free Survival; Neoadjuvant Therapy; Quality of Life; Randomized Controlled Trials as Topic; Triple Negative Breast Neoplasms [drug therapy]

MeSH check words

Female; Humans